

**Receptors Based on Diphenylether and its Aza Analogues for Ion
Recognition using Potentiometry**

A

Thesis submitted in partial
Fulfillment of the requirements for the degree of
Doctor of Philosophy

Submitted by
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Candidate's Declaration

I, hereby declare that the work presented in the thesis entitled **“Receptors Based on Diphenylether and its Aza Analogues for Ion Recognition using Potentiometry”** in partial fulfillment of the requirements for the award of the degree of Doctor of Philosophy at School of Chemistry and Biochemistry, Thapar University, Patiala, is an authentic record of my own work carried out under the joint supervision of Dr. Susheel Mittal CChem FRSC, Senior Professor and Dr. Manmohan Chhibber, Associate Professor, School of Chemistry and Biochemistry, Thapar University, Patiala, India. The matter embodied in this thesis has not been submitted in part or full to any other university or institute for the award of any degree in India or abroad.

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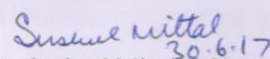
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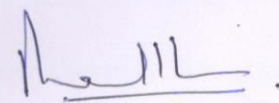

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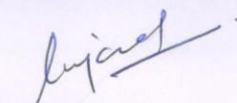
Certified that the thesis entitled **“Receptors Based on Diphenylether and its Aza Analogues for Ion Recognition using Potentiometry”** which is submitted by Ms. Harpreet Kaur in partial fulfillment of the requirements for the award of the Degree of Doctor of Philosophy in the School of Chemistry and Biochemistry, Thapar University, Patiala, is a record of candidate's own independent and original research work carried out by her under our supervision and guidance. The material embodied in this thesis has not been submitted in part or full to any other university or institute for the award of any degree in India or abroad.

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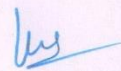
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HARPREET KAUR

ABSTRACT

Few receptor molecules based on the derivatives of di-, triphenylether and their aza analogues were designed, synthesized and characterized as chemical sensors. Ionophoric potential of these receptors was then explored using potentiometric, theoretical and U.V.-Visible studies. All the ionophores were used to fabricate PVC based liquid membrane ISEs for the respective ions. Diphenylether based ionophores were found to be selective towards Fe^{2+} ions, whereas triphenylether derivatives show affinity for Ca^{2+} ions. Diphenylamine based ionophores DPA and TPA were found to show strong complexation with Zn^{2+} and Ni^{2+} , respectively.

The thesis explains the synthesis and spectroscopic characterization of various aryether and arylamine receptors. Ionophoric potential of the receptor molecules have been tested using potentiometric, spectroscopic and theoretical methods. A brief summary of the thesis is given below.

Chapter 1: Introduction

This chapter gives information about different types of sensors with a brief introduction of potentiometric ion selective electrodes. In this, selection of open chain aryether and arylamine based compounds for ion recognition studies using potentiometry have also been discussed. In the end, this chapter shows the structural details of all the ionophores which are synthesized and analysed in the present work.

Chapter 2: Literature Review

This chapter covers the literature survey of acyclic ethers, amines, schiff bases and calixarenes based ionophores, which have been used in the potentiometric and spectroscopic sensing of different type of ions.

Chapter 3: Methodology

This chapter discusses the methodology, which was used to synthesize diphenylethers, triphenylethers, diphenylamine and triphenylamine derivatives. Basic details of different type of analytical techniques like potentiometry, spectrophotometry and quantum chemical studies are provided. Information about all type of materials and instruments used in synthesis or analysis has also been discussed in the chapter.

Reagents were purchased from Sigma Aldrich, LOBA Chemie (India), S.D. Fine (India), and used without further purification. Solvents were distilled before column chromatography. TLC was done on precoated silica gel plates and for the column chromatography silica gel (mesh 100 – 120) was used. For potentiometric studies, high molecular weight polyvinylchloride (PVC), o-nitrophenyloctylether (o-NPOE), sodium tetraphenylborate and tetrahydrofuran (THF) were purchased from Aldrich (India) and used as received. Metal salt solutions of concentration 0.1M were prepared by dissolving AR grade metal salts in double distilled water and standardized

wherever necessary. Working solutions of different concentrations were prepared by serial dilutions.

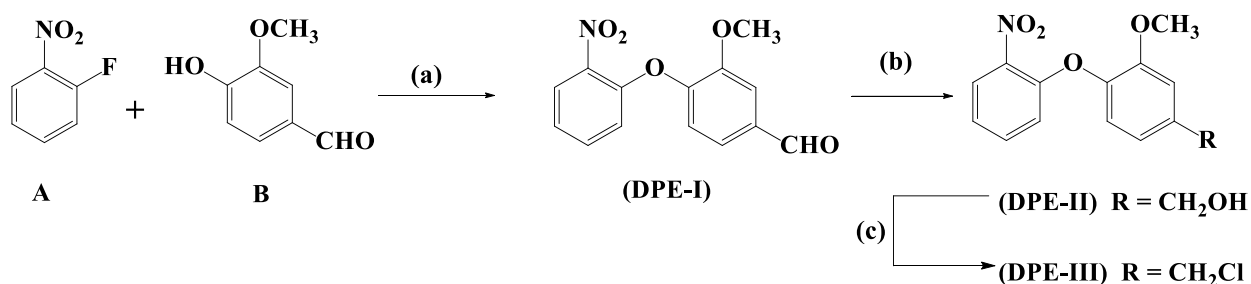
Chapter 4: Results and Discussion

Present study includes the design, synthesis and characterization of some ionophores based on di/triphenyl ethers and di/triphenylamines. Ionophoric potential of these receptors was then explored using potentiometric, theoretical and U.V.-Visible studies.

This chapter is further divided into three sections, which are based on different categories of ionophores as following:

Section 4a: Diphenylethers as Ion Selective Electrodes for Fe^{2+} ions

This section discusses the mechanism of synthesis to prepare diphenylether based receptors named as **DPE-I**, **DPE-II** and **DPE-III** as shown in Scheme 4a.1. Ether linkage was formed via nucleophilic aromatic substitution reaction between an arylhalide and a phenolic derivative using 18-crown-6 as a phase transfer catalyst. All compounds were characterized by ^1H NMR, ^{13}C NMR and Mass spectroscopy techniques.



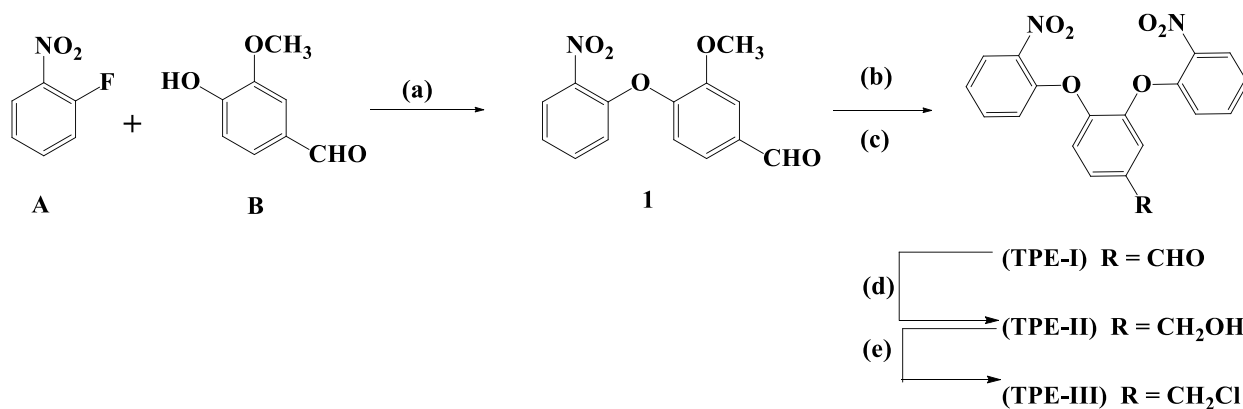
Scheme 4a.1. (a) K_2CO_3 , 18-Crown-6, DMF, RT (b) NaBH_4 , MeOH (c) MsCl , Et_3N , DCM, RT

3-Methoxy-4-(2-nitrophenoxy)benzaldehyde (**DPE-I**), 3-Methoxy-4-(2-nitrophenoxy)benzyl alcohol (**DPE-II**) and 3-methoxy-4-(2-nitrophenoxy)benzylchloride (**DPE-III**) have been explored as neutral carrier ionophores for preparing poly(vinyl chloride) based electrodes selective to **Fe(II)** ions. Based on theoretical studies carried out by density functional theory (DFT) method using Gauss View 4.1.2 software, stability constant determination by sandwich membrane method, U.V.-Visible studies and preliminary potentiometric studies; it has been shown that these ionophores **DPE-I**, **DPE-II** and **DPE-III** were selective for **Fe(II)** ions. Different compositions of the electrode membranes were studied. The best performance in case of **DPE-I** was found with the electrode composition (w/w): ionophore(3) : PVC(33) : o-NPOE(61) : NaTPB(3). This electrode

exhibits Nernstian response with a slope of 27.3 mV/ decade of activity with a detection limit of 6.3×10^{-7} M. The electrode shows satisfactory performance over a pH range of 4-9, with a fast response time of 20s. The best performance in case of **DPE-II** was found with the electrode composition (w/w): ionophore(3) : PVC(33) : o-NPOE(61) : NaTPB(3). The electrode exhibits Nernstian response with a slope of 28.1 mV/ decade of activity with a detection limit of 3.9×10^{-7} M. The electrode shows satisfactory performance over a pH range of 4-9, with a response time of 20s. **DPE-III** showed a slope of 24 mV/decade at 4% ionophore content. In all cases response of the electrodes were highly selective to Fe(II) ions over a number of uni-, di- and trivalent metal ions. The electrodes have been applied successfully for the end point determination of Fe^{2+} in the potentiometric titration and were used as indicator electrodes. Affinity of diphenylethers towards Fe^{2+} ions was further confirmed through U.V.-Visible absorption studies. U.V.-Visible titration was carried out for **DPE-I** and the data was used to calculate detection limits as well as stability constants for Fe(II) ions. Benesi-Hildebrand plot was drawn to calculate the ionophore- Fe^{2+} stoichiometries. Quantum chemical calculations carried out by density functional theory (DFT) method using Gauss View 4.1.2 software provided more insight into the geometry of sensors and their interaction with Fe(II) ions. B3LYP method with 6-31G and LANL2DZ basis sets was employed for the optimization of ionophores independently and along with Fe^{2+} .

Section 4b: Triphenylethers as Ion Selective Electrodes for Ca^{2+} ions

This section discusses the synthetic details as well as potentiometric, spectrophotometric and theoretical analysis of three triphenylether based ionophores. Receptors **TPE-I**, **TPE-II** and **TPE-III** are prepared according to the scheme 4b.1. The first step involved a reaction of commercially available 1-fluoro-2-nitrobenzene(A) and 3-methoxy-4-hydroxy benzaldehyde (B) in DMF in the presence of K_2CO_3 and 18-crown-6 at room temperature to afford diphenylether **1** via nucleophilic aromatic substitution. Another substitution reaction between demethylated product of **1** and **A** generates second ether linkage to give **TPE-I**. Further conversion of TPE-I to corresponding hydroxymethyl and chloromethyl derivatives i.e. **TPE-II** and **TPE-III** was afforded via NaBH_4 – methanol reduction followed by chlorination with mesitylchloride.



Scheme 4b.1. (a) K_2CO_3 , 18-Crown-6, DMF, RT (b) 48% Aq. HBR, CH_3COOH , $120^\circ C$ (c) A, K_2CO_3 , 18-Crown-6, DMF, $100^\circ C$ (d) $NaBH_4$, MeOH (e) MsCl, Et_3N , DCM, RT

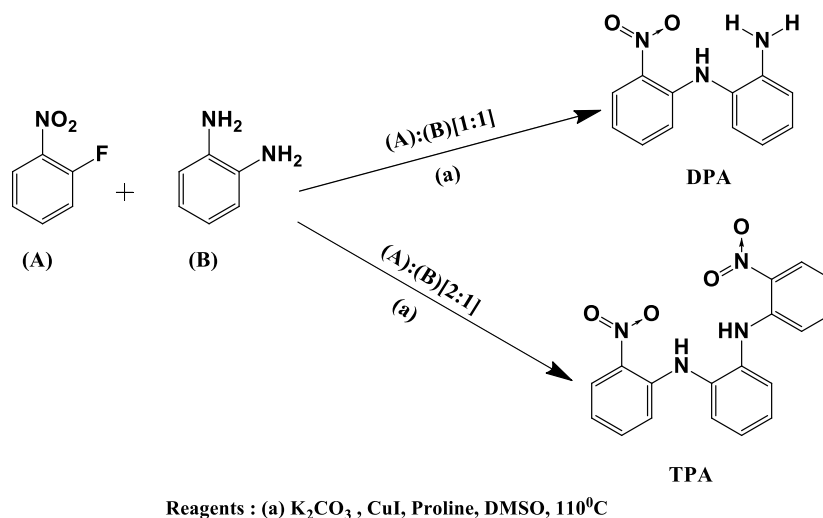
3,4-bis (2-nitrophenoxy) benzaldehyde (**TPE-I**), (3, 4-bis (2-nitrophenoxy)benzylalcohol (**TPE-II**) and (3, 4-bis (2-nitrophenoxy)benzylchloride (**TPE-III**) have been explored as neutral carrier ionophores for preparing poly(vinyl chloride) based electrodes selective to **Ca(II)** ions. Based on theoretical studies carried out by density functional theory (DFT) method using Gauss View 4.1.2 software, stability constant determination by sandwich membrane method, spectrophotometric studies and preliminary potentiometric studies, ionophores **TPE-I**, **TPE-II** and **TPE-III** were found to be selective for **Ca(II)** ions. Different compositions of the membrane were studied in all the three ionophores. In case of (**TPE-I**) the membrane electrode with a composition 33:60:4:3 (PVC: o-NPOE: TPE-I: NaTPB) exhibits Nernstian response towards Ca(II) ions with a slope of 28.5 mV/ decade, with a detection limit of $3.6 \times 10^{-7} M$. Membrane electrode with **TPE-II** also showed best performance with the same membrane composition i.e. 33:60:4:3 (PVC: o-NPOE: TPE-II: NaTPB). Slope observed was 29 mV/decade with a detection limit of $3.2 \times 10^{-7} M$ for Ca(II) ions. The best performance in case of **TPE-III** was found with the electrode composition 33:61:3:3 (PVC: o-NPOE: TPE-III: NaTPB). The electrode exhibits Nernstian response towards Ca(II) ions with a slope of 28 mV/ decade of activity with a detection limit of $7.9 \times 10^{-7} M$. All the three electrodes show fast response time of 15s and a lifetime of four months. The potential response remains almost unchanged over pH range 3-9. All electrodes show good selectivity for Ca(II) ions over other mono-, di- and trivalent metal ions. The electrode response is satisfactory in mixed solvent media up to 20% (v/v) non-aqueous contents.

The proposed membrane electrodes can be used as indicator electrodes for the potentiometric determination of Ca^{2+} in potentiometric titrations. Selectivity of ionophores for Ca(II) ions was

also determined by U.V.-Visible spectroscopy, in acetonitrile-water medium. On the addition of different metal ions Na^+ , Co^{2+} , Al^{3+} , Sr^{2+} , K^+ , Cu^{2+} , Ni^{2+} , Zn^{2+} , Ba^{2+} , Mg^{2+} , Fe^{2+} and Ca^{2+} to a solution of **TPE-I** in acetonitrile – water medium, no significant changes in the UV-Vis spectra were observed except in the case of Ca^{2+} . U.V.-Visible titrations were carried out for the three ionophores and the data was used to calculate detection limits as well as stability constants for Ca(II) ions. Job's plot and Benesi-Hildebrand plot were drawn to calculate the ionophore- Ca^{2+} stoichiometries. Effect of substituents on the binding ability of ionophores was also investigated. Quantum chemical study carried out by density functional theory (DFT) method using Gauss View 4.1.2 software gave more insight into the geometry of sensors and their interaction with Ca(II) ions. B3LYP method with 6-311G basis set was employed for the optimization of ionophores independently and along with Ca^{2+} .

Section 4c: Acyclic arylamines as Ion Selective Electrodes

This section includes the synthesis and ion-recognition properties of di/triphenylamine based receptors. Modified Ullmann reaction, which involves a copper mediated reaction between an arylhalide and an amine in the presence of a bidentate chelator such as amino acids to get the



Scheme 4c.1 Synthesis of Arylamine Ionophores

corresponding arylamine was used to synthesize the receptors. Ionophores **DPA** and **TPA** were synthesised using Scheme 4c.1 by nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene (C) with 2-aminophenylamine (D) in a mole ratio of 1:1 and 2:1 respectively. Contents were

refluxed for 24-30 hours in an aprotic solvent using K_2CO_3 as base, CuI and aminoacid L-Proline as catalysts to afford di and triphenylamines. The two ionophores were then tested for binding with different metal ions by potentiometric and theoretical studies.

Based on formation constant values and preliminary experiments in which **DPA** and **TPA** based PVC membranes were tested for a variety of metal ions, it was concluded that **DPA** showed good response towards Zn^{2+} ions and **TPA** towards Ni^{2+} ions. N-(2-nitrophenyl)benzene-1,2-diamine (**DPA**) as an ionophore has been used to develop as Zinc ion selective electrode. The best performance was observed with an electrode composition (w/w); PVC (33%), 2-nitrophenyloctylether (61%), DPA (3%), NaTPB (3%). The electrode shows a linear dynamic response with a Nernstian slope of 30 mV/decade and a detection limit of $1.3 \times 10^{-6} M$. It has a response time of 15 seconds and can be used for 4 months without any significant divergence in potentials. It can be used in the pH range 3.6-9.3. The electrode response is satisfactory in mixed solvent media up to 20% (v/v) non-aqueous contents. The proposed sensor shows good selectivity with respect to alkali, alkaline earth and transition metal ions. The electrode has been used as an indicator electrode in potentiometric titrations of Zn(II) ions with EDTA. Quantum chemical calculations were carried out for the energy optimization of **DPA** independently and along with Mn^{2+} , Fe^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} . Highest energy decrease of 1778 a.u. was observed for Zn^{2+} , thus indicating a stable complex formation of **DPA** with Zn^{2+} over other metal ions.

In case of Nickel ion selective N, N'-bis(2-nitrophenyl)benzene-1,2-diamine (**TPA**) ionophore, membrane electrode having a composition of TPA : PVC : o-NPOE : NaTPB as 3:32:62:3 wt% shows the best response in terms of slope and the detection limit. In the calibration curve, emf values at varying Ni(II) concentration shows a workable concentration range from $1 \times 10^{-5} M$ to $1 \times 10^{-1} M$ with a Nernstian slope of 30 mV/decade. The detection limit is $2.5 \times 10^{-6} M$ as determined from the intersection of the extrapolated segments of the calibration plot. Response time is measured by recording the emf of the electrode as a function of time. TPA based electrode showed a response time of 20 seconds and a lifetime of about 4 months without observing any considerable change in the electrode characteristics. Non-aqueous tolerance limit goes up to 30% in case of acetonitrile, acetone and 20% in methanol case as far as slope values are considered, though detection limits are slightly affected in acetone medium. The potential values were found to remain unaffected by the change in pH in the pH range 4.2 – 9.2. Selectivity coefficient values reveal that

TPA has reasonably good selectivity for Ni^{2+} ions in the presence of various alkali, alkaline earth and transition metal ions. The proposed membrane electrode can be used as indicator electrode for the potentiometric determination of Ni^{2+} in potentiometric titrations. Theoretical studies were carried out using density functional theory method. B3LYP function with 6-31G basis set was used for quantum chemical calculations of **TPA** independently and along with Ni^{2+} ions on Gaussian 03W programme. The values of energy optimization of uncomplexed and complexed ionophore confirm an overall increase in the stability of system after complexation. Energy decreases from – 1213 a.u. to – 2721 a.u, after addition of Ni^{2+} , thus indicating the formation of highly stable **TPA** – Ni^{2+} complex.

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LIST OF ABBREVIATIONS

Abbreviated Form	Full Form
^1H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
o-NPOE	2- Nitrophenyloctylether
PVC	Polyvinylchloride
NaTPB	Sodium tetra phenyl borate
MPM	Matched Potential Method
FIM	Fixed Inference Method
EDTA	Ethylenediamine tetra acetic acid
THF	Tetrahydrofuran
DFT	Density Functional Theory
UV	Ultra Violet
EMF	Electromotive Force
SCE	Saturated calomel electrode
IUPAC	International Union of Pure & Applied Chemistry
ISE	Ion Selective Electrode

INTRODUCTION

Sensing materials have revolutionized the field of science. There is more and more demand for sensors that can sense species like ions, molecules and gaseous substances present in environment, industrial waste, metabolism by products of pathogens and humans. We can divide sensors into three types, namely:

- (a) Physical sensors for measuring distance, mass, temperature, pressure etc.
- (b) Chemical sensors which measure chemical substances
- (c) Biosensors, which measure chemical substances by using a biological sensing element.

A chemical sensor is a device that responds to a particular analyte in a selective way through a chemical reaction and can be used for the qualitative and quantitative determination of the analyte [1]. There are two parts to a chemical sensor - a region where selective chemistry takes place and the transducer. The chemical reaction produces a signal such as a colour change, emission of fluorescent light, a change in electrical potential at the surface, a flow of electrons, the production of heat, or a change in the oscillator frequency of a crystal. The transducer responds to this signal and translates the magnitude of the signal into a measure of the amount of the analyte.

1.1 Chemical Sensors

Depending on the transducer type, chemical sensors are categorized into the following groups.

Electrochemical sensors:

These include potentiometric sensors (ion-selective electrodes or ISEs), voltammetric and amperometric sensors.

Optical sensors:

In this class of sensors, a spectroscopic measurement is associated with the chemical interaction. They are referred to as optodes.

Mass sensitive sensors:

These make use of the piezoelectric effect. They rely on a change in mass on the surface of an oscillating crystal which shifts the frequency of oscillation. The extent of frequency shift is a measure of the amount of material adsorbed on the surface.

Heat sensitive sensors:

They are also known as calorimetric sensors; here, the transducer monitors the heat of a chemical reaction involving the analyte.

1.2 Electrochemical transducers

There are three main types of electrochemical sensors: potentiometric, amperometric and conductometric [2-7]. For potentiometric sensors, a local equilibrium is established at the sensor interface, where either the electrode or membrane potential is measured and information about the composition of a sample is obtained from the potential difference between two electrodes. Amperometric sensors exploit the use of a potential applied between a reference and a working electrode, to cause the oxidation or reduction of an electroactive species and the resultant current is measured. On the other hand, conductometric sensors are involved with the measurement of conductivity at a series of frequencies.

1.3 Classification of potentiometric sensors

Based on the physical state of the substances forming the electrode membrane [8, 9] potentiometric sensors are classified into:

Ion-selective electrodes with solid membranes:

The membrane can be either homogeneous (a single crystal, a crystalline substance or a glass which is considered to be a solid with regard to the immobility of the anionic groups) or heterogeneous, where a crystalline substance is built into a matrix made from a suitable polymer.

Ion-selective electrodes with liquid membranes:

In this case, the sensor membrane is represented by a water-immiscible liquid in which a substance is dissolved, which is capable of exchanging the ion in solution for which the sensor is selective.

Another classification based on the membranes used in potentiometric sensors are:

a. Glass membranes

The membrane is composed of a silicate glass and is selective to ions such as H^+ , Na^+ etc.

b. Sparingly soluble inorganic salt membranes

This type consists of a section of single crystal or the pressed powdered disc of an inorganic salt which is seen to show selectivity to certain ions.

c. Polymer-immobilized ionophore membranes

In these, an ion-selective complexing agent or ion-exchanger is immobilized in a plastic matrix such as poly (vinyl chloride).

d. Gel-immobilized and chemically bonded enzyme membranes

These membranes use the highly specific reactions catalyzed by enzymes. The enzyme is incorporated into a matrix or bonded onto a solid surface.

1.4 Potentiometric transducer

Potentiometric transducer constitutes one type of electrochemical transducers. Potentiometric sensors based on plasticized PVC membranes doped with neutral carriers have been extensively developed for many ions [10-14]. These are based on ion selective electrodes (ISEs). It is an electrode, designed to respond to one particular ion more than others. It usually responds to the species according to the Nernst equation i.e.,

$$E = E^{\circ} \pm \frac{RT}{ZF} \ln a_x$$

Here,

E is the potential,

E° is the standard potential of the cell,

R is the gas constant,

T is the absolute temperature,

F is the Faraday constant,

a_x is the activity of ion and

Z is the charge on ion.

ISE is a potentiometric device, i.e., the potential of the electrode, measured against an appropriate reference electrode, is proportional to the logarithm of the activity of the ion being tested. Such a device usually responds rapidly, with a linear range of about 10^{-6} to 10^{-1} M for most ISEs. It operates on the principle of a concentration cell [15-20], in which it contains a selective membrane, which develops a potential if there is a concentration difference across the membrane of the ion being tested.

1.5 Polymeric Membrane Ion Selective Electrodes

Any polymeric membrane ISE consists of different components including an ionophore, the nature and the amounts of which greatly affect the characteristics of the sensor. These components include the polymeric matrix, the ionophore, the membrane solvent mediator and the ionic additive.

Polymer matrix

Generally, the membrane components are supported by an inert lipophilic matrix, where the solvent mediator acts as a plasticizer providing the required final features to the membrane [21]. Various type of matrices like soft polyurethanes with a low content of crystalline units [22], silicone rubber [23], poly (vinylidene chloride) [24] and polysiloxanes [25] have been reported to be used in the membrane construction. However, PVC is the one which is mostly used [26-30]. Polymer matrix provides mechanical strength to the membrane and has no chemical interaction with the target ion.

Ionic Additives

An important feature of membrane used in ISEs is Donnan exclusion or permselectivity, which means that the membrane is permeable only for ions with the same charge sign of the measuring ion. This feature is must in order to get a theoretical Nernstian response of the electrode. Lipophilic salts are used as ionic additives to develop this membrane characteristic as well as to lower the electrical resistance of the membrane [31]. Normally, a tetraphenylborate derivative is used as a lipophilic salt for cation selective membranes, whereas anion selective membranes use a tetraalkylammonium salt for this purpose.

Membrane solvent

Membrane solvents (plasticizers) are used to increase the plasticity of membrane, which is required to give a homogeneous organic phase. This ingredient also affects the selectivity

behaviour of the ISE membrane. A plasticizer change from the polar *o*-NPOE or nitrobenzene (NB) to the apolar dibutyl phthalate (DBP), for example, is reported to reduce the M^{2+} -selectivity [32]. More polar solvents prefer divalent over monovalent ions [33]. The nature of the plasticizer also strongly influences the measuring range of the ion-selective sensors. Another factor, highly influenced by the membrane solvent, is the formation of the ion-pairs. The amount of ion-pairs formed between the complexed ions and the lipophilic counter ions, which is known to influence the slope of the response curve, is predicted to be negligible in the polar membranes, while this is significant in the case of non-polar membranes. Plasticizers which can be potentially used in potentiometric membrane are as follows: Benzyl acetate(BA), bis(2-hydroxyethyl) phthalate (BEHP), bis(1-butylpentyl) adipate (BBPA), dioctyl phthalate (DOP), bis(2-ethylhexyl) sebacate (BEHS), dibenzyl ether (DBE), dibutyl phthalates (DBP), dibutylsebacate (DBS), 2-nitrophenyl phenyl ether (*o*-NPPE), 2-nitrophenyl octyl ether (*o*-NPOE) and tri-*n*-butyl phosphate (TBP).

Ionophore

The key component of any ion selective membrane is the ionophore or electroactive component which imparts the selectivity and enables the ISE to respond selectively to a particular analyte, thus avoiding interferences from other substances. Ionophore structure must contain sufficient number of lipophilic groups so as to keep its leaching rate from membrane phase to sample phase as low as possible.

1.6 Mechanism of Ion selective electrodes

The potentiometric sensors make use of an electrochemical cell that is constituted of two galvanic half-cells: the ion-selective electrode and a reference electrode. The measured EMF of the cell at zero current is the sum of local potential differences, arising at each electrochemical interface. The ion-selective membrane is usually placed between two aqueous solutions, one being the so-called internal solution and the other is the sample solution. Three models have been proposed to explain the response mechanism of ISEs; the kinetic model, the membrane surface model and the phase boundary model [34-38].

The kinetic model is based on the transport of ions across the membrane and relates the mobility of ions to the selectivity of the ISE. The membrane surface model assumes that only the processes occurring at the membrane surface are relevant for the potential, which is

generated across the sample-membrane interface and is the result of ion-selective charge separation at the interface. However, the phase boundary model uses the thermodynamic equilibria and the electroneutrality condition within aqueous and organic membrane phases to explain the emerging potential at the interface. In most of the cases, the response of ISEs can be described by the phase-boundary potential, E_{PB} , which is directly related to the spontaneous equilibrium partitioning of ions across the sample membrane interface and can be calculated as follows

$$E_{PB} = E^0 \pm \frac{RT}{zF} \ln \frac{a_1(aq)}{a_1(org)}$$

Where z is the charge and R , T , F have their usual meaning.

$$E^0 = \frac{\mu^0(aq) - \mu^0(org)}{zF}$$

μ^0 and a_1 being the standard potentials and the ion activity in the respective phases.

The activity of uncomplexed ion, $a_1(org)$, in the membrane can be calculated by phase-boundary potential model. If $a_1(org)$ does not depend on $a_1(aq)$, the ISE response has a Nernstian slope of 59/ x mV/decade. Any deviations from this slope can be described by changes of $a_1(org)$ with $a_1(aq)$ or by differences between $a_1(aq)$ at the membrane surface and in the bulk of the sample.

1.7 Recognition and supramolecular chemistry

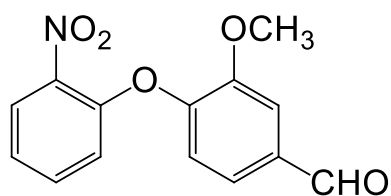
Ion selective sensors are based on the selective recognition of one specific ion over other similar ions. This recognition is based on the principles of supramolecular chemistry which is commonly known as host-guest chemistry [39]. According to this, the principle of sensing materials is based upon the fact that a host or a sensor molecule can recognize guest molecules in a very selective way using weak and generally reversible noncovalent bonds [40]. In practice, host is either an organic building block or a bio-molecule that can hold a guest which is a cation, anion or a neutral molecule. Among the guest molecules, cations such as sodium, potassium, magnesium and calcium are ubiquitous in biological systems. Some transition metal ions such as Cu(I or II), Co(II), Zn(I) and Mn(II) play important roles in metalloenzymes and other proteins [41]. Organic chemistry provides an excellent tool to design and synthesize

receptors that can accommodate charged or neutral species selectively. Thus, a considerable effort has been devoted to the synthesis of chemical sensor systems based on noncovalent interactions, including hydrogen bonding, pi-pi bonding, donor-acceptor, electrostatic, hydrophobic, hydrophilic and coordination-based interactions [42-44]. A number of motifs, including crown ethers, cryptands, aza-crowns, polyamines and carboxylic acid derivatives have been designed, synthesized and studied as cation complexants and their selectivity is highly dependent on structure.

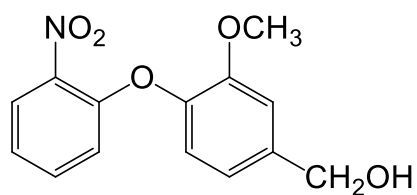
1.8 Diphenylether unit as a receptor

Rapid development in the synthesis of neutral macrocyclic ligands capable of complexing with cations and anions has stimulated research efforts in many fields of chemistry. The pioneering work of Pederson on macrocyclic polyethers or crown ethers [45-47] was chiefly concerned with oxygen-containing ring systems and produced a series of powerful receptors for alkali and alkaline earth metal cations. Nitrogen is often incorporated into these structures and may predominate when binding to transition metals is the object. In most of these macrocycles, the hetero atoms are separated by a carbon containing unit of two or more atoms. Replacement of this aliphatic two carbon unit that separates hetero atoms by aromatic systems like benzene, naphthalene or pyridine would impart rigidity as well as planarity to the receptor molecule and hence will affect the selectivity. In general, the receptor properties of a host molecule are determined by a delicate balance between the pre arrangement of donor atoms due to certain “rigidity”(required for high selectivity) and the ability to adapt to the target guest by a sufficient “flexibility”(for a sufficiently fast ion exchange). Aryl containing macrocyclic compounds impart reasonable rigidity due to planar aromatic ring and sufficient flexibility, if they are open chain ethers. Considering this, acyclic arylethers seem to offer both flexibility as well as the rigidity. Further, the affinity for metal cations is also regulated by the character of the donor atoms contained in the ionophore framework [48]. While the hard nature of oxygen donor atoms favour the formation of complexes with alkali and alkaline earth metal cations, incorporation of nitrogen donor atoms is attractive, as it alters the binding tendency of ionophores so that they may more readily complex cations of transition metals [49]. Thus, both arylether and arylamine based receptors were chosen for the study. Also, there were not many reports where open chain arylether or arylamine based ionophores have been used as potentiometric ion selective electrodes. Thus, we have designed and synthesized

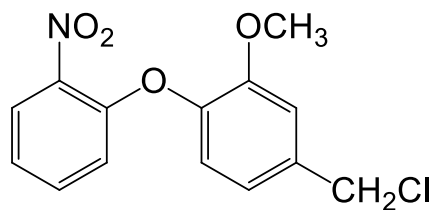
few diphenylethers and their aza analogues as ionophores, which were used in fabrication and characterization as potentiometric ion-selective electrodes for metal ions. Keeping in view that, the selectivity and behaviour of the ionophore can be modified by steric and electronic variation in the region of the donor atom [50], the synthesized compounds were improvised by varying the substituents on phenyl rings to get better membrane characteristics.



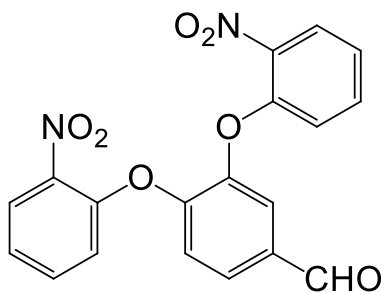
**3-Methoxy-4-(2-nitrophenoxy) benzaldehyde
(DPE-I)**



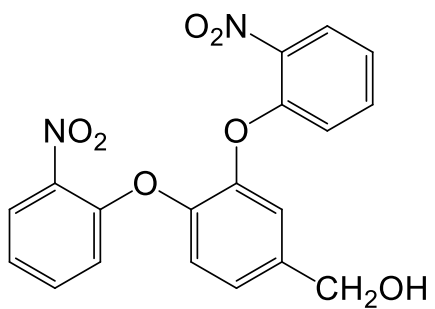
**3-Methoxy-4-(2-nitrophenoxy) benzylalcohol
(DPE-II)**



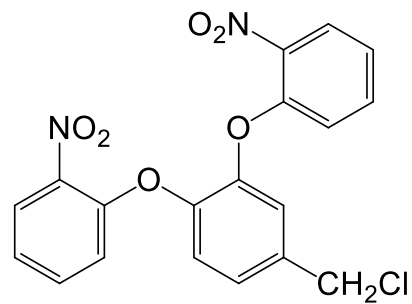
**3-Methoxy-4-(2-nitrophenoxy) benzylchloride
(DPE-III)**



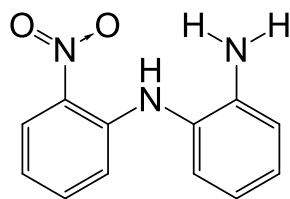
**3, 4-bis (2-nitrophenoxy) benzaldehyde
(TPE-I)**



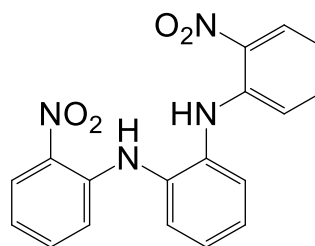
**3, 4-bis (2-nitrophenoxy)benzylalcohol
(TPE-II)**



**3, 4-bis (2-nitrophenoxy)benzylchloride
(TPE-III)**



**N-(2-nitrophenyl)benzene-1,2-diamine
(DPA)**



**N,N'-bis(2-nitrophenyl)benzene-1,2-diamine
(TPA)**

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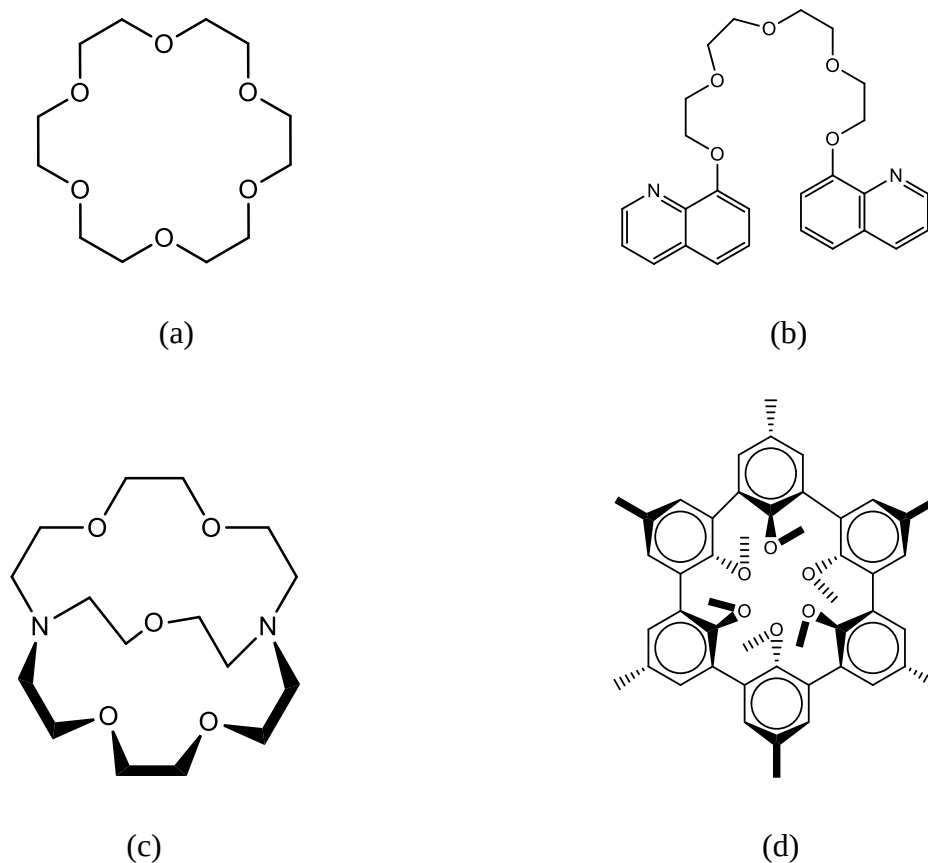
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LITERATURE SURVEY

Selective recognition and sensing of ions by artificial receptors have attracted a considerable research interest in terms of their applications in various areas [1-5]. In order to develop an artificial receptor that is selective toward a specific analyte, multiple interactions between host and guest in a complementary fashion have to be considered. Several strategies can be followed in the design of artificial receptors with finest selectivity toward a particular ion. Organic chemistry provides an excellent tool to design and synthesize receptors that can accommodate charged or neutral species selectively.

Macrocyclic compounds are mostly uncharged organic molecules that contain a cavity in which a cation or an anion can be encapsulated. The complexes thus formed are of great analytical interest. Although their synthesis was reported as early as late thirties [6], their complexing properties with cations were not recognized until Pedersen [7] published his first paper on crown ethers under the title “Cyclic Polyethers and Their Complexes with Metal Salts” in 1967. This was followed by Lehn et al. [8], who synthesized another series of macrobicyclic compounds called cryptands which further led to the development of tricyclic and tetra cyclic compounds. Although the discovery of crown ethers and cryptands profoundly benefited the fields of anionic synthetic reagents, phase-transfer catalysis, and biological ion transport, it was the property of compounds to complex with cations that gave Pedersen, Lehn, and Cram the Nobel Prize in 1987.

The discovery by Pedersen, Lehn, Cram and the mechanism of many natural ionophores brought in the application of carrier based ion-selective electrodes (ISEs) that have evolved to a routine analytical technique now. In fact, the first neutral ionophores used in ISE membranes were antibiotics [9, 10]. It is estimated that in the United States about 200 million clinical assays of K^+ are made every year with valinomycin-based ISEs. ISEs are mainly utilized for monitoring biologically relevant ions besides in many other fields, including physiology, process control, and environmental analysis. They, thus form one of the most important groups of chemical sensors.



(a)Crown ethers (b) Podands (c) Cryptands (d) Spherands

Figure 2.1 Some synthetic ionophores

In general, synthetic ionophores can be classified into a) Crown ethers b) Podands c) Cryptands and d) Spherands on the basis of their molecular structures. Whereas crown ethers are cyclic structures which were accidentally discovered by Charles Pedersen, podands are acyclic hosts with pendant binding sites. Podands exhibit less cation affinity and lower binding selectivity than crown ethers, but are much easier prepared. Cryptands are three dimensional analogous of crown ethers and have higher affinity for metal ions. Due to their comparatively complex structures they require more number of steps for their synthesis than crown ethers or podands. Spherands are another class of host compounds. Compared to crown ether and cryptands, which have a rather flexible structure in solution, spherands are rigid. Figure 2.1 shows the structures of different ionophores discussed above. As can be seen, all type of

ionophores are cyclic except podands, which are open chain analogues of macrocyclic crown ethers. Ever since their discovery, it is probable that the number of examples of different macrocycles that have been synthesized is above 10000 [11]. Most of these structures are alkyl ethers, alkyl amines, alkylthia ethers or a combination of these. A representative example of their structures is given in Figure 2.2.

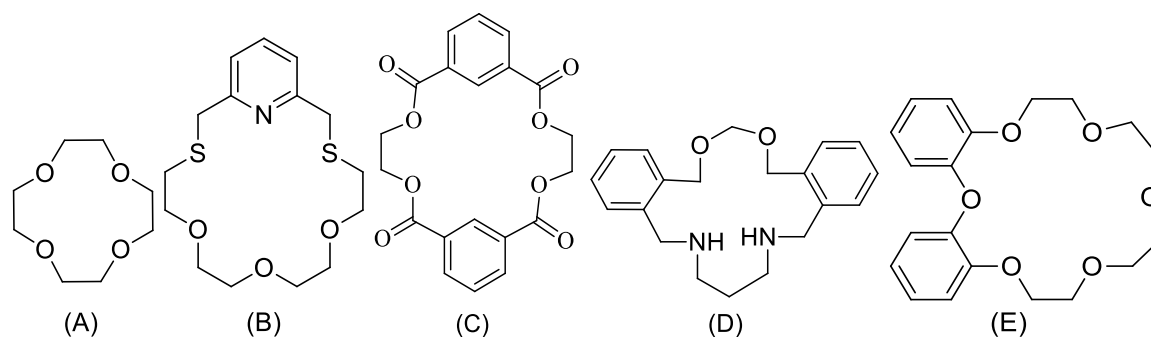


Figure 2.2 Structural variations in crown ethers

The diaryl ether unit as shown in (E) (Figure 2.2) is a common structural feature in several natural products like antibiotic vancomycin, antitumoral bouvardin, perrottetines, riccardin B as well as in synthetic weed killing chemicals [12-16]. In addition, poly (aryl ethers) are significant commercial polymers [17] (Figure 2.3).

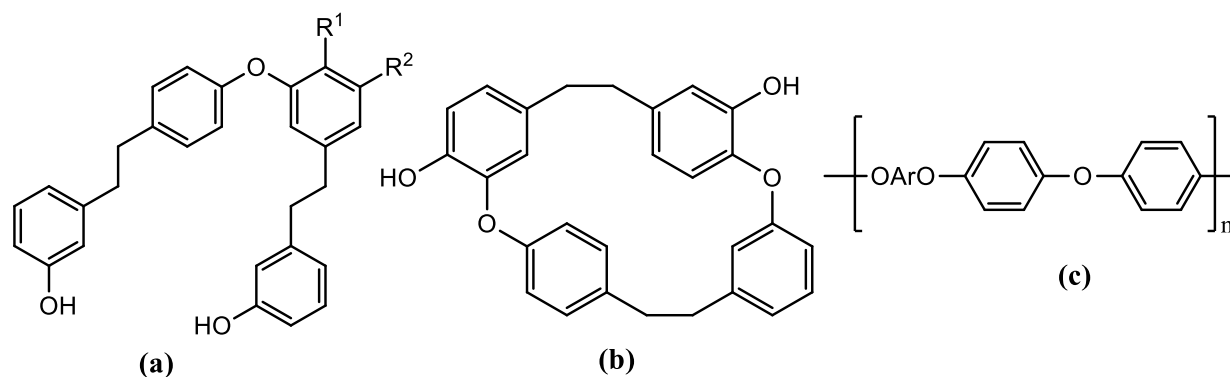
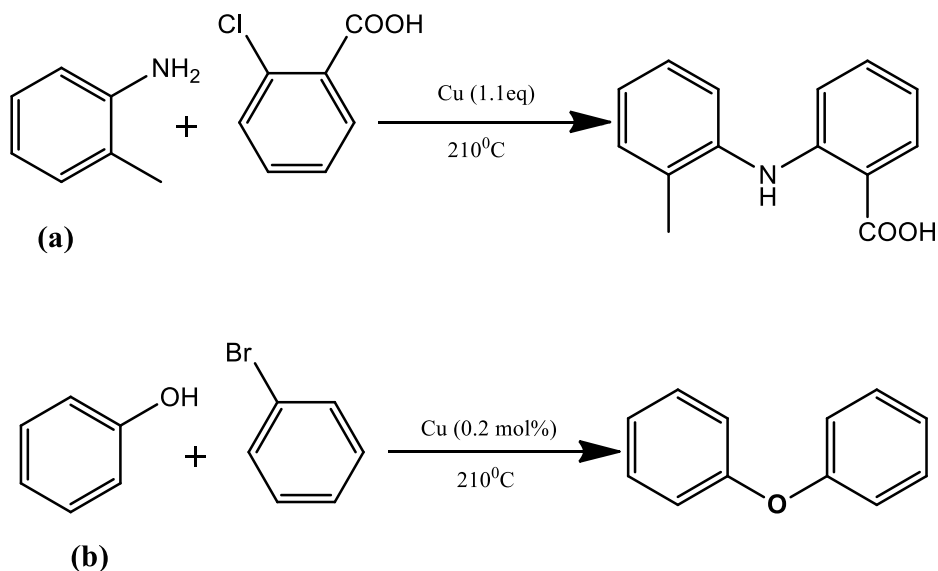


Figure 2.3 Structures of few naturally occurring and synthetic products containing diphenylether unit (a) Perrottetines (b) Riccardin B (c) Commercial polymer

A lot of efforts have been put in to synthesize diarylether/amine moieties and find their usefulness in various fields. The literature below describes the recent developments in their synthesis starting from the earlier procedures.

2.1 Synthesis of diarylethers/amines

The synthesis of diaryl ethers or its aza analogues was not an easy job in earlier attempts, especially if the target molecule was sensitive to the harsh reaction conditions used. The most straight forward way to synthesize diaryl ethers involved the direct formation of an aryl-oxygen bond from an aryl halide [18]. A few years after the discovery of the classic Ullmann reaction in 1901, the copper-mediated arylation of aromatic amines or phenols with aryl halides (Scheme 2.1 a, b) appeared to be the method of choice for the synthesis of N-aryl amines and aryl ethers [19, 20], but required harsh conditions like high temperature, strong bases, long reaction time, stoichiometric amounts of copper reagent, electron-poor aromatic substrates and high-boiling polar solvents. Besides that, there were problems related to the solubility of many Cu compounds, hence excess amounts of Cu had to be used [21].



Scheme 2.1 Ullmann condensation for the synthesis of
(a) diarylamines and (b) diarylethers

Substantial efforts of the past few years have yielded improved Ullmann O- and N-arylation methods. Several research groups showed that certain additives, which probably act as copper ligands [22], increase reaction rates, lower the reaction temperature and allow the coupling in

the presence of reduced amounts of copper. Thus, ligands such as ethylene glycol diacetate, 8-hydroxyquinoline, 1-naphthoic acid, triphenylphosphine, or 2,2,6,6-tetramethylheptane-3,5 dione [23-27] were successfully used as promoters. It was proposed that such additives probably increase the solubility of copper salts [28] as well as could also enhance reactivity by increasing electronic density on the catalytic species. In spite of all these advances, Ullmann ether formation methods still required high temperatures of at least 100°C [29] and in some cases high catalyst loading [27]. Ma [30] proposed that amino acids like *N,N*-dimethylglycine as a ligand could lower the reaction temperature to 90°C. Cristau et al. [31] reported an efficient method for the synthesis of diaryl ethers under particularly mild conditions using oxime and Schiff base type ligands (Figure 2.4). These inexpensive ligands were found to greatly accelerate the Ullmann-type coupling of aryl bromides or iodides with phenols and gave excellent yields in the presence of Cs₂CO₃, catalytic copper(I) oxide and acetonitrile. It was observed that the yields in Cu catalyzed methods were strongly sensitive to the nature of ligand, base type and solvent used.

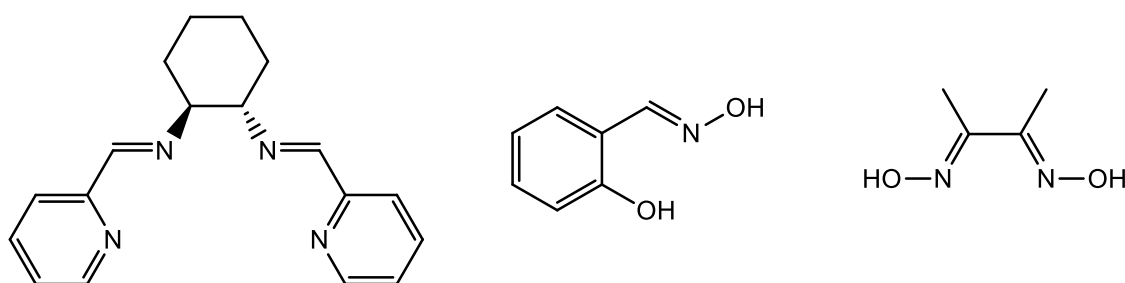
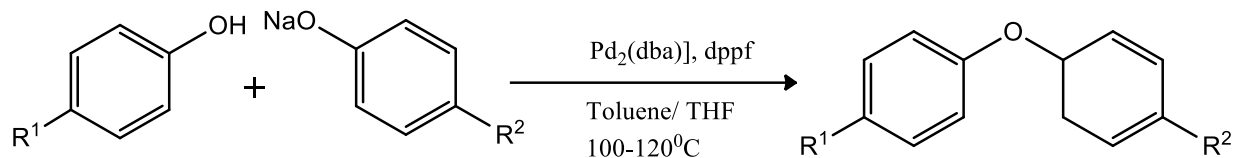


Figure 2.4 Schiff base ligands used in Ullmann-type coupling

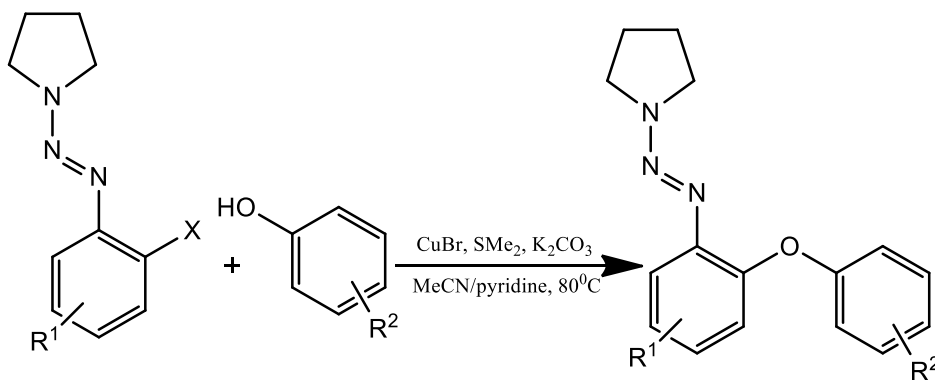
Evans et al. [32] and researchers at Du Pont [33] recommended the use of alternative arylating agents like aryl boronic acids in the presence of copper(II) acetate, triethylamine or pyridine and molecular sieves for an optimum reaction temperature.

A palladium-catalyzed coupling between sodium phenoxides and electron-deficient aryl bromides had been reported by Mann et al. [34]. Reaction was based on an *in-situ* ligand exchange of dibenzylideneacetone (dba) with 1,1'-diphenylphosphanylferrocene (dppf) (Scheme 2.2).



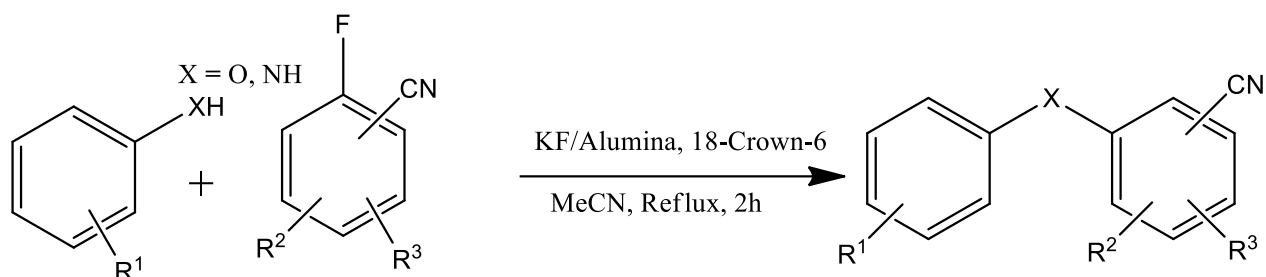
Scheme 2.2 Pd catalyzed synthesis of diarylethers

Another approach used by several groups was to increase the reactivity of aryl halides towards phenoxides through suitable substitutions. The use of an activating ortho-nitro group in the synthesis of diaryl ethers by Eicher et al. [35] reduced the reaction time to less than one hour. Zhu et al. [12] reported that phenoxides react smoothly at room temperature when ortho-nitrofluoro arenes are used as electrophiles. However, this method requires subsequent reduction and deamination steps in order to remove the nitro group unless the target molecule bears this functional group. Nicolaou et al. [36] proposed that Aryl bromides and iodides substituted with ortho-triazene react smoothly with phenols at 80°C in the presence of K_2CO_3 and $CuBr/Me_2S$ to afford diaryl ethers in good yields (Scheme 2.3).



Scheme 2.3 Diarylether formation by ortho-activation of haloarenes

Otherwise, chloroarenes can also be activated through their π complexes with manganese, iron, or ruthenium, that react at low temperature with phenoxides to yield diaryl ethers [37]. Sawyer et al., [38] reported an efficient alternative to the Ullmann synthesis of diaryl ethers and diarylamines involving the $SNAr$ mechanism by the addition of a phenol or aniline to an appropriate aryl halide, mediated by potassium-fluoride, alumina and 18-Crown-6 in acetonitrile or DMSO (Scheme 2.4).



Scheme 2.4 Coupling of phenols and anilines to substituted aryl fluorides using KF as base and 18-crown-6 as phase transfer catalyst

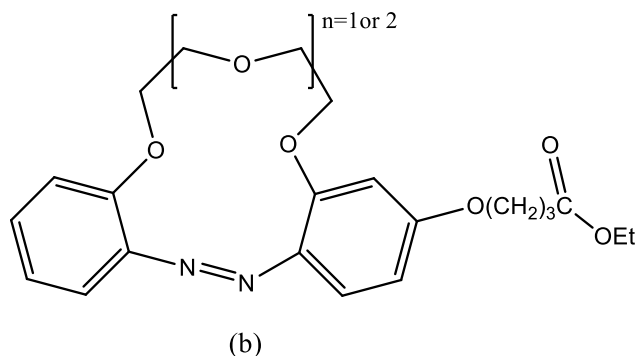
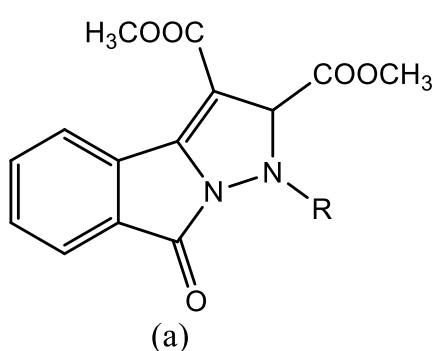
Present work has employed the same methodology with slight modification for the synthesis of aromatic C-O bond and modified Ullmann condensation for the formation of aromatic C-N bond to synthesize acyclic diphenylether and diphenylamine based ionophores.

A comparison of crownethers with their acyclic analogues i.e., podands in terms of ion selectivity and stability of resulting complex will undoubtedly go in favour of crown compounds due to their more preorganized structures [39] as well as “macrocyclic effect”. But in one important aspect in which flexibility of podands makes them superior to the cyclic analogues is the kinetics of complexation and decomplexation of cations. A general observation is that higher the rigidity or preorganisation of host molecule, slower will be the formation or decomposition of resulting host-guest complex. Thus, both the complexation and decomplexation rates of the podands are higher than the macrocycles. This property of podands makes them more useful in ion transport, sensing and other promising fields of application. Chemical modification of these acyclic hosts like changing the chain length or the donor atom can result in a change of selectivity and thus podand receptors can form complexes with cations ranging from alkali and alkaline earth metals to transition metals [40]. As a recognition motif, podand based receptors have been reported to be used successfully as recognition components in electrochemical sensors [41, 42] and spectrophotometric sensors [43-45]. Here, we present important contribution of research activities in recent years that focus on potentiometric and spectrophotometric sensors based primarily on oxygen and nitrogen containing acyclic hosts as well as few macrocycles.

2.2 RECEPTORS FOR MAIN GROUP METALS

2.2.1 Potentiometric sensors

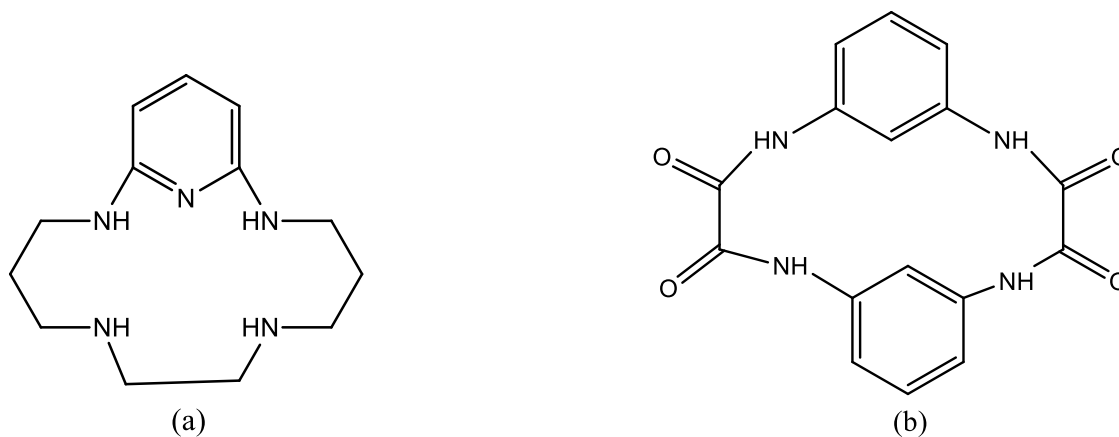
Zamani et al., [46] have reported ionophore dimethyl 1-acetyl-8-oxo-2,8-dihydro-1H-pyrazolo[5,1-a]isoindole-2,3- dicarboxylate as a Ba(II) selective electrode. The electrode exhibited a Nernstian slope of 29.7 mV per decade with a detection limit of 7.6×10^{-7} M between pH 3.0 and 11.0. The proposed sensor was selective for Ba(II) over a variety of other metal ions. Ganjali et al., [47] reported a highly selective and sensitive Be(II) sensor based on 4-nitrobenzo-9-crown-3-ether (NBCE). Nernstian response over a wide concentration range (1.0×10^{-4} to 1.0×10^{-10} M) was observed with a detection limit of 3.5×10^{-11} M. The electrode was also used in the direct determination of beryllium ions in beryl and binary mixtures as well as an indicator electrode in the potentiometric titration of Be^{2+} ions with EDTA. Wyszeccka et al., [48] reported the synthesis and ionophoric properties of new 13- and 16-membered azobenzo crownethers. It was observed that oxyalkylester and oxyalkylamide derivatives are very good potentiometric sensors with 13-membered rings showing preference for Na(I) and 16-membered rings showing preference for K(I). All the electrodes show near nernstian slope values with good detection limits of the order of 10^{-6} M for Na^+ ions and 10^{-7} M for K^+ ions. Electrodes with 13-membered ion-carriers are more pH sensitive in relation to primary ion than those containing their 16-membered analogs.



(a) Ba(II) selective ionophore[46] and (b) azobenzo crownethers based alkali metal ionophores [48]

A PVC based membrane sensor containing N,N'-bis(salecylidene)-1,2-phenylenediamine (salophen) as membrane carrier was prepared and investigated as Al(III) selective electrode by Gholivand et al., [49]. The sensor was found to exhibit a Nernstian response toward Al(III) over a wide concentration range (8.0×10^{-7} to 3.0×10^{-2} M), with a detection limit of 6.0×10^{-7} M. Very fast response time and high selectivity was observed for Al^{3+} in comparison with alkali, alkaline earth and some heavy metal ions.

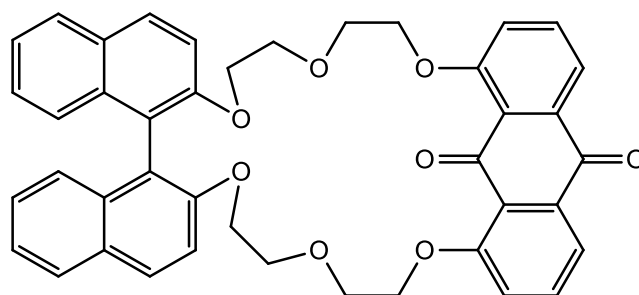
Kim et al., [50] used thiacalix[4]biscrownethers with 1,3-alternate conformation as ionophores for cesium selective electrodes. A linear response with a slope of 57.6 mV/decade in the concentration range of 1.0×10^{-6} to 3.2×10^{-2} M was observed over a wide pH range of 2.5 – 12.5. Another cesium selective electrode was reported by Peper et al., [51] in 2005 by doping polyethylene glycol into a PVC matrix containing sodium tetrakis-[3,5-bis(trifluoromethyl) phenyl]borate (TFPB) as the ion exchanger. Electrode showed a slope of 55.4 mV/decade with a detection limit of approximately 1.0×10^{-6} M. In the same year, Singh et al., [52] reported 2,3,4-pyridine-1,3,5,7,12-pentaazacyclopentadeca-3-ene as a Ba(II) selective electrode. Slope of 30 mV/decade with a linear range of 1.4×10^{-6} to 1.0×10^{-1} M was observed. Electrode showed excellent selectivity over competitive metal ions. Also, a Sr(II) selective electrode was reported [53] using 5,7,12,14-dibenzo-2,3,9,10-tetraoxa-1,4,8,11-tetraazacyclotetradecane as an ionophore, which could detect Sr^{2+} ions up to a limit of 2.82×10^{-6} M. The electrode exhibited a slope of 29 mV/decade over a concentration range of 3.98×10^{-6} to 1.0×10^{-1} M with a stable potential in the pH range of 2.5 – 10.5.



(a) Ba(II) selective ionophore [52] and (b) Sr(II) selective ionophore [53]

Gupta et al., [54] proposed benzo-15-crown-5 as an ion carrier for Mg(II) ions. The electrode could be used for a period of 4 months with a Nernstian slope over a linear range from 1.0×10^{-5} to 1.0×10^{-1} M of Mg^{2+} ions. The electrode revealed good selectivities with respect to many alkali, alkaline earth and transition metal ions. A Na(I) selective electrode [55] based on 1-methyl-1-vinyl-14-crown-5 was also reported by same authors. The proposed sensor displayed a slope of 55 mV/decade with a detection limit of 2.8×10^{-6} M. It worked well within pH range of 6.5 – 9.5 with good selectivity relative to common metal ions. Mittal et al., [56] reported a calcium selective electrode by incorporating dibenzo-18-crown-6 in a PVC membrane. Slope of 28.0 mV/decade with a detection limit of 4.0×10^{-6} M was exhibited by the electrode, which had a life time of 5 months.

Binaphthyl-based crown ethers incorporating anthraquinone, benzoquinone, and 1,4-dimethoxybenzene were reported as Rb^+ selective ionophores in the poly(vinyl chloride) (PVC) membrane by Hyun et al., [57]. The membrane containing NPOE gave a better selectivity than those containing either DOA or BPPA as a plasticizer. The sensor responded within a linear range of 1.0×10^{-5} to 1.0×10^{-1} M with a slope of 54.7 mV/decade. Detection limit for Rb(I) was determined as 9.0×10^{-5} M. The ISE membrane exhibited good selectivity for Rb^+ ions over ammonium, alkali and alkaline earth metal ions.

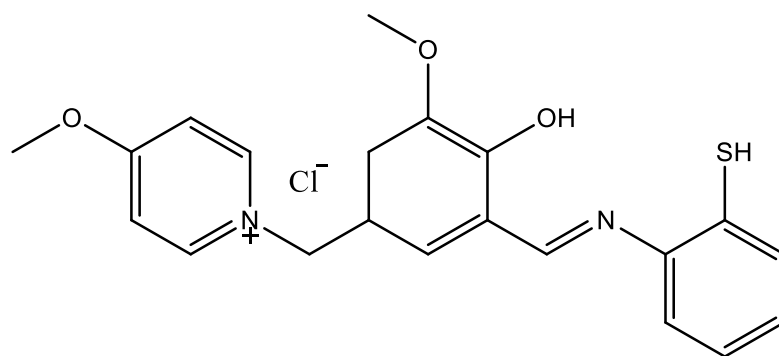


Binaphthyl-based Rb (I) selective ionophore [57]

2.2.2 Spectrophotometric sensors

Optical chemosensors for various metal ions have attracted much interest because of their prospective applications in environmental detection, molecular catalysis and biological fluorescence imaging, etc [58]. In spectrophotometric sensors, the cation–ligand interactions are well manifested by color and UV–vis spectral changes. Selective detection of biologically

important cations such as Na^+ , K^+ , Mg^{2+} and Ca^{2+} is of great importance for understanding cell physiology. The detection of Ca(II) ions in blood or serum has attracted a lot of attention because of the high importance value of these ions in the diagnosis of several types of diseases and Ca^{2+} concentration fluctuations play a critical regulatory role in several biological systems. Wang et al., [59] reported a thioether linked bichromophoric squaraine containing three sulphur atoms as a highly selective Ca^{2+} sensor. The selective binding of Ca^{2+} resulted in an absorption blue shift and fluorescence quenching due to the cation-induced folding of the bichromophore and the resultant exciton coupling between the squaraine chromophores. Job's plot confirmed a 1:1 binding between the sensor and Ca^{2+} . Anions such as oxalate can extract Ca^{2+} from squaraine foldamers and restore the fluorescent signal. Recently, Saleh et al., [60] have developed a water-soluble chemosensor, based on the ionic Schiff-base, 1-(4-methoxy-3-((2-mercaptophenylimino)methyl)-5-methoxybenzyl)-4-methoxy pyridinium chloride to fluorescently sense Ca(II) ions. High degree of selectivity and sensitivity was observed for Ca(II) ions over other physiologically relevant alkali, alkaline-earth and transition metal ions.

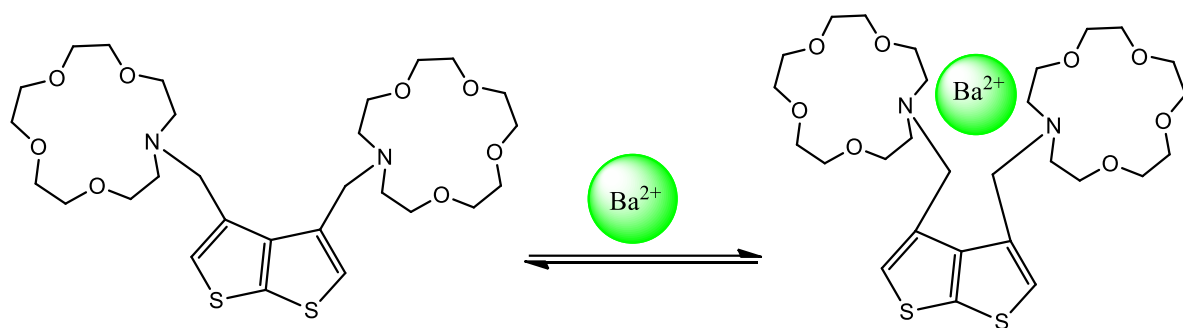


Schiff-base based Ca(II) selective ionophore [60]

Lee et al., [61] reported a ratiometric fluorescent metal ion sensor based on 15-crown-5-ether for K^+ ions. Fluorescence titration with different metal ions at a pH of 8.3 showed a change in the fluorescence intensity. This sensor system can act as a good probe for sensing applications especially in biological systems. Spectrophotometric sensors for alkali metal cations based on calix[4]arene derivatives having phenanthridine moieties were reported by Bakic et al., [62]. Complexation of these derivatives with alkali-metal cations was studied by means of fluorimetric, spectrophotometric and potentiometric techniques. It was found that

the cation-binding affinity of ligand with four phenanthridine subunits was much higher than other ligands. The ligands were found to show strong complexation with sodium and potassium ions.

Bis(crown ether) derivatives, in which two crown ether moieties are linked by a flexible aliphatic chain, in some cases form more stable complexes with metal cations and show a higher cation binding selectivity compared to the monocyclic analogues. Wu et al., [63] proposed one such fluoroionophore based on 3,4-dimethylthieno[2,3-b]thiophene bearing two monoaza-15-crown-5 ethers at 3- and 4-positions. UV–Vis and fluorescence responses of the compound upon the addition of alkali and alkaline earth metal cations were evaluated in acetonitrile solution. Receptor showed unique response for Ba^{2+} due to the formation of an intramolecular sandwich complex.

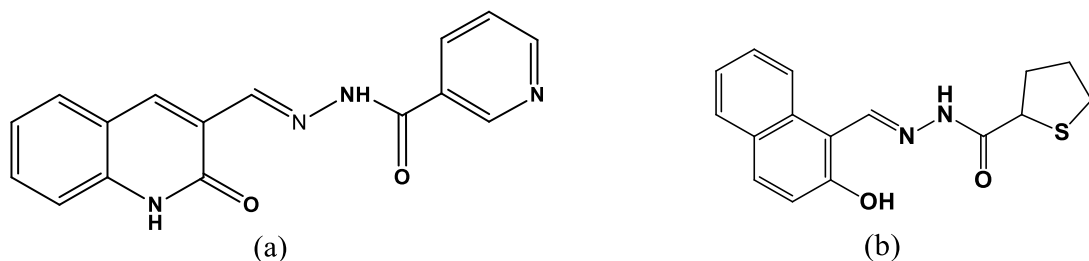


Bis(crownether) derivative forming an intramolecular sandwich complex with Ba(II) [63]

Citterio et al., [64] reported an optical sensor for Li^+ ions based on tetramethyl substituted 14-crown-4 ether derivative. The ionophore showed high selectivity for Lithium ions with binding-induced blue shift in the fluorescence spectra. The sensor can be applied to quantitative measurements of lithium in clinical samples, although possible interference from Na^+ has to be considered at the lower therapeutic level of Li^+ .

In 2014, a new water-soluble rhodamine-based Al^{3+} ion-selective probe was developed by Sen et al., [65]. Proposed sensor specifically binds Al^{3+} ions with a visually observable change from colorless to pink in electronic spectral behavior, making it possible to detect the presence of Al^{3+} ions with the naked eye. The addition of Al^{3+} ions to a solution of sensor in HEPES buffer at 25 °C, resulted in a decrease of fluorescence intensity at $\lambda_{\text{em}} = 470 \text{ nm}$, while a new

peak at $\lambda_{em} = 588$ nm increased gradually. The detection limit for Al^{3+} ions was estimated to be 6.19×10^{-9} M. Another Al^{3+} sensor was reported by Zhang et al., [66]. Sensor, based on a Schiff-base derived from 2-oxo-quinoline-3-carbaldehyde exhibited a high selectivity and sensitivity toward $Al(III)$ ions over other commonly existing metal ions in ethanol, and the detection limit of Al^{3+} ions is at the parts per billion level (0.67 ppb.). The mass spectra and Job's plot confirmed the 1:1 stoichiometry between ionophore and Al^{3+} .



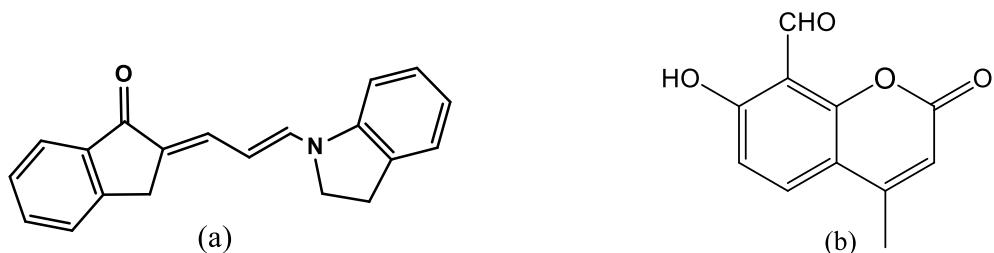
(a) 2-oxo-quinoline-3-carbaldehyde based [66] and (b) Hydrazide [67] based $Al(III)$ selective ionophores

Tiwari et al., [67] reported a 2-thiophene carboxylic acid hydrazide based Al^{3+} selective chemosensor(E)N-[(2-hydroxy-naphthalen-1-yl)methylene]thiophene-2-carbohydrazide. Proposed sensor selectively and sensitively detects Al^{3+} ions without any interference from common cations by a strong fluorescent change in ethanol–water medium.

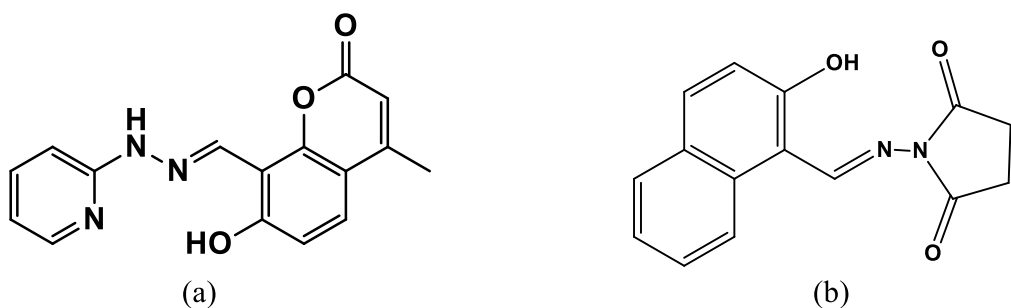
In biological systems, magnesium ion plays a crucial role. Different types of sensors are available for its detection. Few spectrophotometric sensors for Mg^{2+} ion developed in the recent past are discussed here. Sardar et al., [68] have proposed an acyclic conjugated dye similar to a ketocyanine dye as an optical sensor for Mg^{2+} ions. The sensor forms a 1:1 complex with different alkaline earth metal cations as indicated by the appearance of new bands at a longer wavelength. All the metal ions under study showed enhancement of fluorescence intensity, which was found to depend on the concentration range of the metal ion. For Mg^{2+} ion, the enhancement was observed at μM range whereas other ions require a much higher concentration.

Another $Mg(II)$ sensor 4-Methyl-7-hydroxy-8-formyl Coumarin was reported by Gupta et al., [69]. The binding ability of the sensor was investigated through UV-Vis. Absorption,

fluorescence and electrochemical studies. A good binding constant with a detection limit of 0.43 μM was observed for Mg^{2+} ions.



A fluoroionophore for Mg^{2+} ion based on 2-pyridylhydrazone and 7-hydroxycoumarin was reported by Hernandez et al., [70]. 1:1 complex formation between ionophore and Mg^{2+} ions lead to a fluorescence enhancement. The chemosensor showed good binding ability towards Mg^{2+} with an association constant of $5.57 \times 10^4 \text{ L mol}^{-1}$, a relatively low interference from Ca^{2+} and a low detection limit of 105 nmol L^{-1} in ethanol water solution.



Liu et al., [71] reported a fluorescent chemosensor (E)-1-((2-hydroxynaphthalen-1-yl)methyleneamino)pyrrolidine-2,5-dione for Mg^{2+} ions. Upon binding with Mg^{2+} , the UV – visible absorption spectra displayed an isosbestic point at 374 nm. The sensor also exhibited turn-on fluorescence response for Mg^{2+} ions in alcohol solvent with high sensitivity and selectivity. Wysiacka et al., [48] presented a detailed report of spectrophotometric behaviour of 13- and 16-membered azobenzocrown ethers having aromatic amino, aromatic amide,

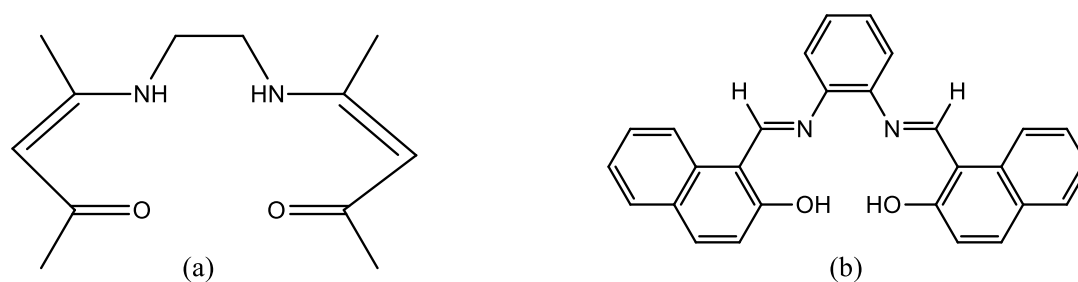
ether–ester and ether–amide substituents at para position to an azo group. Spectroscopic studies showed that not only macrocycle size, but also nature of the substituent in benzene ring strongly influences metal cation selectivity and the stability constant values of their alkali and alkaline earth metal complexes in acetonitrile. 13-Membered aminoazobenzocrown shows Mg^{2+} selective spectrophotometric response in acetonitrile.

2.3 RECEPTORS FOR TRANSITION METALS

2.3.1 Potentiometric sensors

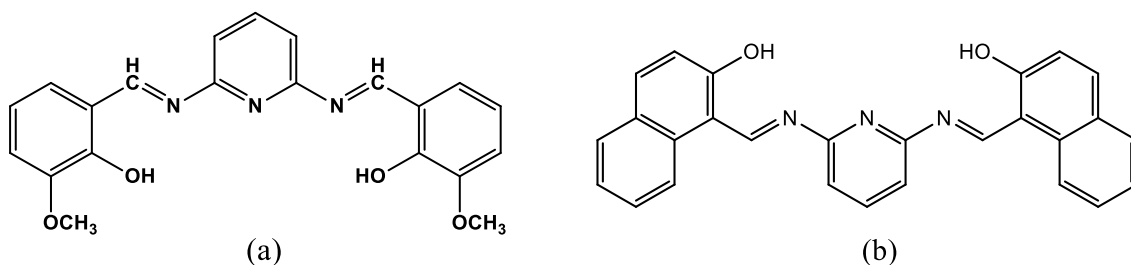
Besides the fact that some transition metal ions are essential to many organisms in small doses, high doses affect the ecosystem and human health, and in the case of very toxic metals even small doses can be hazardous to human health. The importance of controlling the level of environmental pollution in natural water ways and potable water has generated increasing interest in the development of novel potentiometric sensors for the detection of heavy metals.

Zinc occurs naturally in air, water and soil, but zinc concentrations are rising unnaturally due to addition of zinc through human activities. Various types of Zn^{2+} -selective electrodes have been reported so far by different research groups. Zinc(II)-selective electrode based on N,N-bis(acetylacetone)ethylenediimine was reported by Gupta et al., [72], the best result for which was obtained for the electrode membrane of composition I:PVC:NaTPB:NPOE(5:100:6:200), showing a Nernstian response (30.0 mV/decade) and a workable concentration range of 1.0×10^{-6} to 1.0×10^{-1} M. Hosseini et al., [73] reported a highly selective and sensitive zinc ion selective membrane electrode based on N, N-phenylenebis(salicylideaminato). The membrane is composed of PVC, o-nitrophenyl octylether (NPOE) as plasticizer, potassium tetrakis(p-chlorophenyl)borate as lipophilic ionic additive, and the said ionophore as the sensing material. The proposed electrode displayed a Nernstian response to Zn^{2+} ions over a wide concentration range of 5.0×10^{-7} to 1.0×10^{-1} M with a slope of 29.4 mV/decade and a detection limit of 2.6×10^{-7} M. The selectivity coefficients for mono-, di-, and trivalent cations indicate the good selectivity over a large number of cations.



(a) Ethylenediamine based [72] and (b) Schiff base based [73] Zn (II) selective ionophores

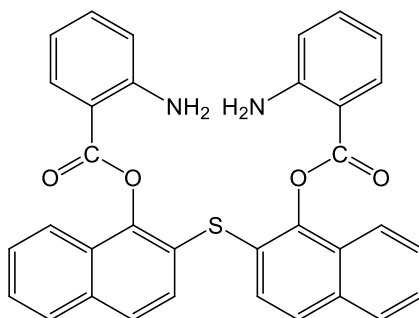
Singh et al., [74] reported Zn(II) selective polymeric membrane electrode based on a macrocycle 6, 7: 14,15-BzO₂-10,11- (4-methylbenzene)- [15]- 6,8,12,14-tetraene-9,12-N₂-1,5-O₂. Several membranes having different compositions of PVC, plasticizers, ionic additives and ionophore were fabricated and the best response was observed for the membrane having composition I:PVC:TBP:NaTPB in the ratio of 4:37:57:2 (w/w; mg). The electrode exhibited Nernstian slope for Zn²⁺ ions with limits of detection of 3.3×10^{-7} mol L⁻¹ and a response time of 12 s. Fu et al., [75] reported a Schiff base as ionophore for preparing PVC based membrane sensors selective to Zn²⁺ ions. The effect of plasticizers on electrode was also studied. The electrode revealed Nernstian behavior over a concentration range of 1.0×10^{-6} to 1.0×10^{-3} M and a workable pH range of 3.4 – 5.8. Another Zn²⁺ ion selective sensor based on N, N-bis(2-hydroxy-4-methoxybenzaldehyde)-2,6-diaminopyridine was reported by Mizani et al [76]. The sensor displayed a linear dynamic range between 1.0×10^{-7} to 1.0×10^{-1} M, with a Nernstian slope and a workable pH range of 4.5 – 10. Khorshid et al. [77] reported chemically modified carbon paste sensors based on Zn-acetaldehyde thiosemicarbazone (Zn-ATSC) and Zn-thiosemicarbazide (Zn-TSC) complexes for selective detection of Zn²⁺ ions. The constructed sensors showed linear Nernstian slopes 32.5 and 28.5 mV per decade over the concentration range of 5.0×10^{-8} to 2.0×10^{-3} M and 6.3×10^{-8} to 7.9×10^{-3} M with a detection limit of 0.25 and 0.50 nM for (Zn-TSC) and (Zn-ATSC) ions, respectively.



(a) Pyridine based [76] Zn (II) selective ionophore and (b) Schiff base based [79] Pb (II) selective ionophore

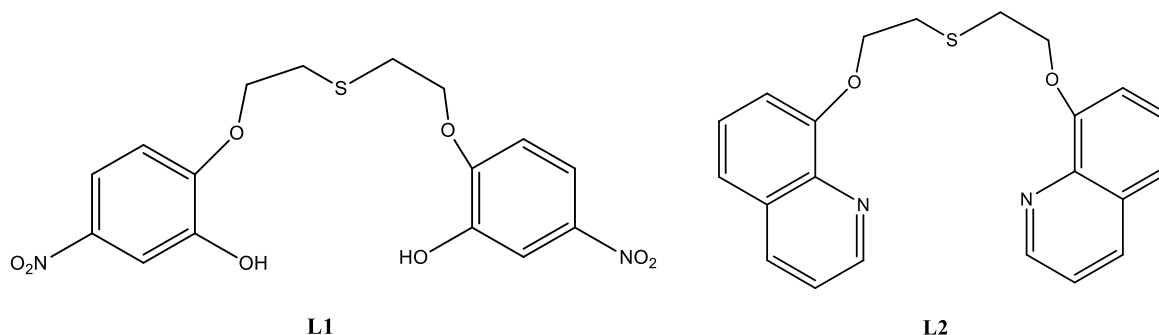
Lead is ubiquitous in the environment and is hazardous. The use of ion-selective electrodes for the detection of lead has received much interest, and many ligands have been investigated as sensing agents in electrodes based on ionophore-doped PVC membranes. *N, N'*-dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane was prepared and developed as a Pb(II) selective sensor by Gupta et al., [78]. Nernstian response over a wide concentration range of 8.2×10^{-6} to 1.0×10^{-1} M with a slope of 30.0 mV/decade of activity of Pb^{2+} ions was observed. Sensor exhibited a response time of 10 s, life time of 3 months, a working pH range of 2–6.8 and was used as an indicator electrode in potentiometric titration of lead ions with EDTA. Gupta et al., [79] reported another Pb^{2+} -selective electrode based on Schiff base *N,N*-bis(2-hydroxy-1-naphthalene)-2,6-pyridiamine. The sensor worked well in the concentration range of 3.2×10^{-6} to 1.0×10^{-1} M with a Nernstian slope. Ion et al., [80] fabricated a Pb^{2+} -selective sensor from PVC matrix membranes containing the ionophore 3,7,11-tris(2-pyridylmethyl)-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15- triene. The membrane with the composition of I:PVC:o-NPOE:KTpClPB in the weight percentage ratio of 2:32:60:6 exhibited the best performance, having a slope of 28.5 mV/decade in the concentration range 1.0×10^{-6} to 1.0×10^{-1} M, a response time of 20 s and very good selectivity for Pb^{2+} ions. The high selectivity in the presence of Cd^{2+} may be important for further studies. A binaphthyl based ionophore 1,1'-thiobis(naphthalene-2,1-diyl)bis(2-aminobenzoate) [81] was synthesized and used as a carrier for construction of Pb^{2+} modified carbon paste electrode. The sensor exhibited significantly enhanced selectivity toward Pb^{2+} ion over the concentration range 8.0×10^{-8} to 1.0×10^{-2} mol L⁻¹ with a lower detection limit of 5.0×10^{-8} mol L⁻¹ and a Nernstian slope of 29.0 mV/decade of lead activity. The interaction

between ionophore and Pb^{2+} was studied spectrophotometrically and it exhibited that the stoichiometry of the complex was 1:1 in acetonitrile solution.



Binaphthyl based Pb(II) selective ionophore [81]

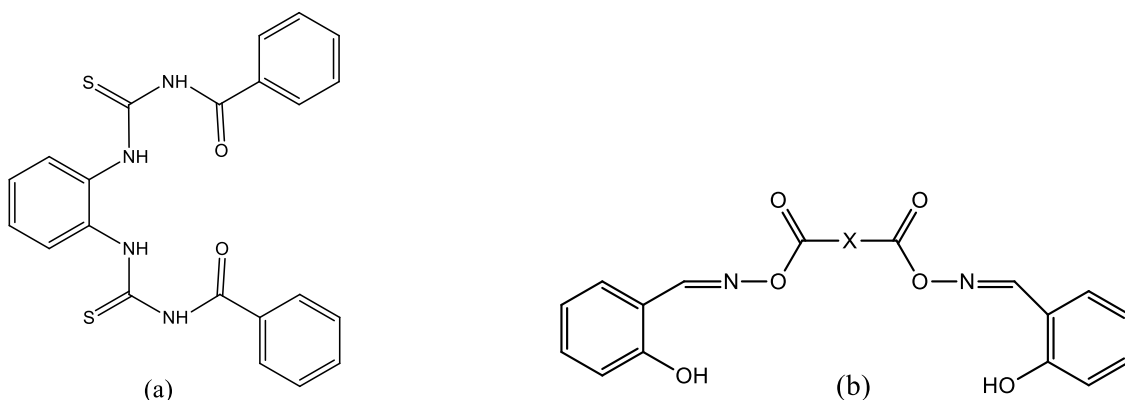
Singh et al., [82] reported two diethylsulphide based chelates 1,5-bis(2'-hydroxy-4'-nitrophenoxy)-3-thiapentane (L1) and 1,5-bis(8'-oxybenzopyridine)-3-thiapentane (L2) as Pb(II)-selective PVC membrane electrodes. The addition of anionic additives and various plasticizers was found to improve the performance of the electrode. The best performance was obtained with the electrode having a membrane of ionophore (L1) with the composition PVC:o-NPOE:ionophore(L1):NaTFPB (%w/w) of 33 : 62 : 3 : 2. The electrode exhibited Nernstian response with a slope of 31.57 mV/decade of activity in the concentration range from 2.0×10^{-9} – 1.0×10^{-1} M, with a fast response time of 5 s. The electrode can be used as indicator electrode for the titration of Pb^{2+} ion with EDTA and in sequential titration of Pb^{2+} with mixture of some inorganic anions.



Diethylsulphide based chelates [82] selective for Pb(II).

In 2014, Pazik et al., [83] reported the synthesis and potentiometric characterization of tetrazole dipodaland tripodal ligands containing amide groups. Their selectivity and

sensitivity were studied towards alkali, alkaline earth, transition and heavy metal cations. The polymeric electrodes containing diamide ionophores, which have propyl linker between aryl moieties were found to be selective towards Cd^{2+} ions. Electrode displayed good detection limit and selectivity coefficients with a linear response in Cd^{2+} concentration of 10^{-5} – 10^{-2} M and a pH range of 3–11. On the other hand, electrodes based on ionophores with tripodal derivatives and diamides having two carbon cyclic or acyclic linker displayed more sensitive responses to Pb(II) ions. These sensors exhibited linear response with a near Nernstian slope of 25–29 mV/dec within the concentration range of 10^{-6} – 10^{-2} M and 10^{-5} – 10^{-2} M and the limit of detection was determined to be below 10^{-6} M. The electrodes were suitable for use in aqueous solutions and responded within 20 s. Another highly sensitive and selective potentiometric PVC-membrane sensor for Pb(II) ions containing 2-Bis(N-benzoylthioureido)benzene as an ionophore was reported by Abraham et al., [84]. Slope of 30.4 mV/decade with a linear range from 6.3×10^{-8} to 4.0×10^{-2} M and a detection limit of 2.5×10^{-8} M was observed. Selectivity coefficients were determined by the matched potential method (MPM). The sensor was used to measure Pb(II) ions in raw milk and in potentiometric titration.

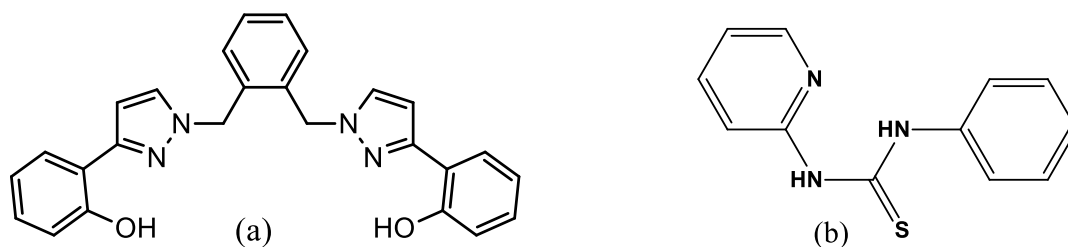


(a) Thiourea based [84] Pb(II) selective ionophore and (b) Schiff base based [85] Cr(III) selective ionophore

Chromium (III) is an essential nutrient for humans. Shamsipur et al.,[85] synthesized Schiff bases and studied their ability as Cr^{3+} ion carrier in PVC-membrane electrodes. The polymeric membrane (PME) and coated glassy carbon (CGCE) electrodes based on 2-hydroxybenzaldehyde-O,O-(1,2-dioxetane-1,2-diyl) oxime displayed Nernstian response for

Cr³⁺ ion, with a linear dynamic range of 1.5×10^{-6} to 8.0×10^{-3} M for PME and 4.0×10^{-7} to 3.0×10^{-3} M for CGCE. Limit of detection was 1×10^{-6} M for PME and 1×10^{-7} M for CGCE. Another Cr³⁺-selective sensor based on 5-amino-1-phenyl-1H-pyrazole-4-carboxamide was fabricated by Zamani et al., [86]. The demonstrated characteristics of the sensor included a linear slope of 19.6 mV/decade, a detection limit of 5.3×10^{-7} M and a very good selectivity for Cr³⁺ ion with a fast response time of 10 s. The developed sensor provided satisfactory results of Cr³⁺ determination in biological samples and also in waste water of the chromium electroplating industry. Kumar et al., [87] fabricated a highly selective Cr(III) sensor based on 2-(1-(2-((3-(2-hydroxyphenyl)-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazol-3-yl)phenol (I). Effect of various plasticizers on the electrode performance was investigated. The optimum composition of the best performing membrane contained (I):KCITPB:NPOE:PVC in the ratio 15 : 3 : 40 : 42 w/w. The sensor exhibited near Nernstian slope of 20 mV/decade of activity in the working concentration range of 1.2×10^{-7} to 1.0×10^{-1} M, a response time of 10 s and a life time of about 5 months. Sensor was successfully used to determine Cr(III) concentration in the industrial waste samples.

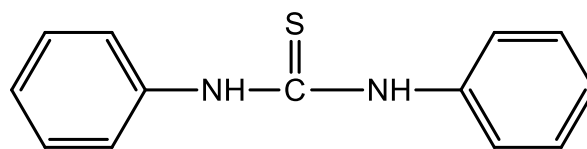
Fe³⁺ is another metal that has attracted the attention of analytical chemists. Babakhanian et al., [88] used a new ionophore 1,1-(iminiobis(methan-1-yl-1-ylidene))dinaphthalen-2-ol to develop Fe(III)-PVC membrane sensor. The best performance was observed for the membrane composition having 33% PVC, 65% TEHP, 1% NaTPB and 1% ionophore. A linear potential response was observed with a detection limit of 5.0×10^{-8} M and a Nernstian slope of 19.9 mV/decade. Special advantages of the sensor were its high selectivity towards Fe³⁺ ions, response time of less than 12 s. Mollagh et al., [89] fabricated PVC membrane and coated wire sensors based on 1-phenyl-3-pyridin-2-ylthiourea for Fe³⁺ ions with a linear dynamic range between 3×10^{-7} to 1×10^{-2} M and a slope of 20.2 mV/decade.



(a) Acyclic phenol based [87] Cr (III) selective ionophore and (b) Thiourea based [89] Fe (III) selective ionophore

Bera et al., [90] reported a PVC-incorporated membrane electrode selective for iron(III) based on cis,cis-1,3,5-tris{(2-hydroxybenzyl)aminomethyl}cyclohexane. Sensor exhibited a slope of 19.4 mV/decade with a detection limit of 7.0×10^{-6} M. The potentiometric selectivity coefficients calculated using match potential method (MPM) indicated high selectivity for Fe^{3+} ions among different cations.

Mercury, due to its toxic nature has also inspired the development of suitable sensors. A liquid membrane, Hg^{2+} ion-selective electrode based on 1,3-diphenylthiourea as ionophore was developed by Perez-Marin et al., [91]. Due to the the presence of the complex $\text{Hg}(\text{OH})^+$ ion, slope of 58.6 mV/decade in the concentration range 6.0×10^{-6} to 5.0×10^{-4} M was observed. The ISE showed stable detection reproducibility during six weeks and a high selectivity for Hg^{2+} ions against common ions. A second linear response curve for Hg^{2+} was obtained at pH 4 with a slope of 30.8 mV/decade in the concentration range 2.0×10^{-6} to 2.1×10^{-4} M.

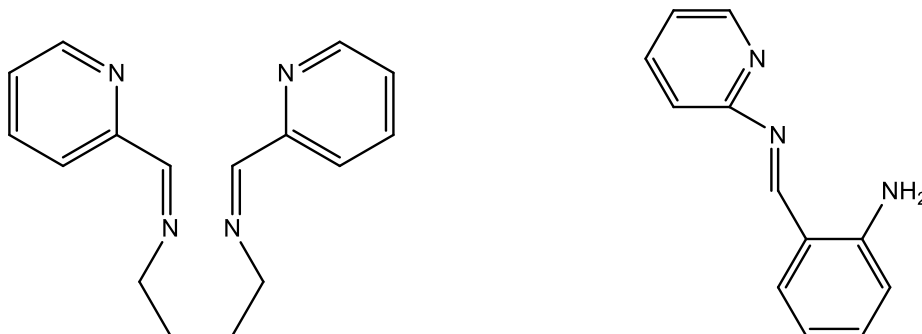


1,3-Diphenylthiourea as $\text{Hg}(\text{II})$ selective ionophore [91]

Ensafi et al., [92] reported another PVC membrane potentiometric sensor for Hg^{2+} ions. The membrane having bis(benzoyl acetone)diethylene triamine as an electroactive material, exhibited a linear response to Hg^{2+} ions with a detection limit of 3.7×10^{-7} M and a slope of 29.8 mV/decade. The sensor was highly selective over a large number of mono-, bi-, and trivalent cations. Hajiaghababaei et al., [93] developed a Hg^{2+} -selective sensor using oxime-2-(*N*-pyperidino methyl) cyclohexanone as ionophore. Sensor exhibited a Nernstian response for Hg^{2+} ions with a detection limit of 6.3×10^{-7} mol L^{-1} and a slope of 29.4 mV per decade.

Cadmium exists in industries as an inevitable by-product of zinc, lead, and copper extraction. After being applied, it enters the environment mainly through the ground, because it is found in manures and pesticides. Gupta et al., [94] developed cadmium selective membrane sensors as a comparative analysis based on N, N-[bis(pyridine-2-yl)formylidene]butane-1,4-diamine

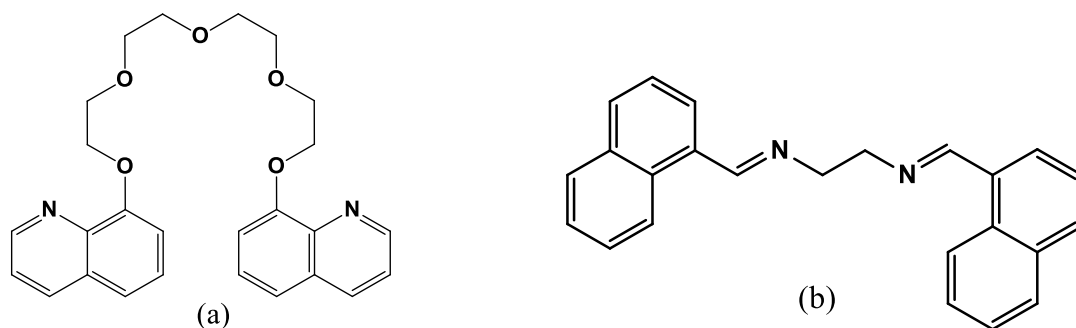
and N-(2-pyridinylmethylene)-1,2-benzenediamine. The sensors displayed wide concentration range of 7.9×10^{-8} to 1.0×10^{-1} M with slope of 30.0 mV/decade and 1.3×10^{-6} to 1.0×10^{-1} M with a slope of 28.0 mV/decade respectively.



Cd (II) selective ionophores based on two Schiff bases [94]

In the past few years, need for the determination of cadmium and other heavy metals has increased because of growing environmental problems. Cadmium is known as highly toxic element. Ghaemi et al., [95] developed a new Cd(II) ion selective sensor using 1,13-bis(8-quinolyl)-1,4,7,10,13-pentaoxatridecane as an ionophoric carrier. The membrane solution containing ionophore was directly coated on the surface of graphite rod. A good linear response for Cd^{2+} with a Nernstian slope of 29.8 mV/decade and a detection limit of 8.4×10^{-6} M was observed for the sensor. The sensor was used as an indicator electrode for potentiometric titration of Cd^{2+} ions as well as for determination of Cadmium ions in real water samples.

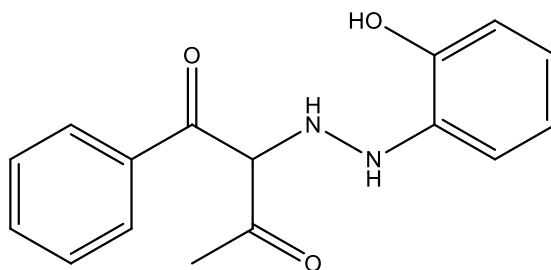
Kumar et al., [96] proposed a PVC membrane ion selective electrode selective towards Ni(II) ions using a Schiff base containing a binaphthyl moiety as the ionophore. The sensor displayed a Nernstian response for nickel ions with a lower limit of detection of 1.3×10^{-6} M and can tolerate the presence of 25% (v/v) methanol or ethanol. Proposed sensor was used as an indicator electrode in the potentiometric titration of Ni(II) ions against EDTA and also for the direct determination of nickel content in effluent samples, chocolates and hydrogenated oils.



(a) Quinoline based [95] Cd (II) selective ionophore and (b) Ni (II) selective ionophore based on Schiff base [96]

Zamani et al., [97] developed a PVC membrane containing 5-methoxy-5,6-diphenyl-4,5 dihydro-3(2H)-pyridazinethione as an ionophore, which exhibited a Nernstian response for Ni^{2+} ions with a detection limit of 6.7×10^{-7} M and exhibited a fast response time (<15 s). The sensor presented very good selectivity and sensitivity towards the Ni^{2+} ions over a wide variety of cations, including alkali, alkaline earth, transition, and heavy metal ions.

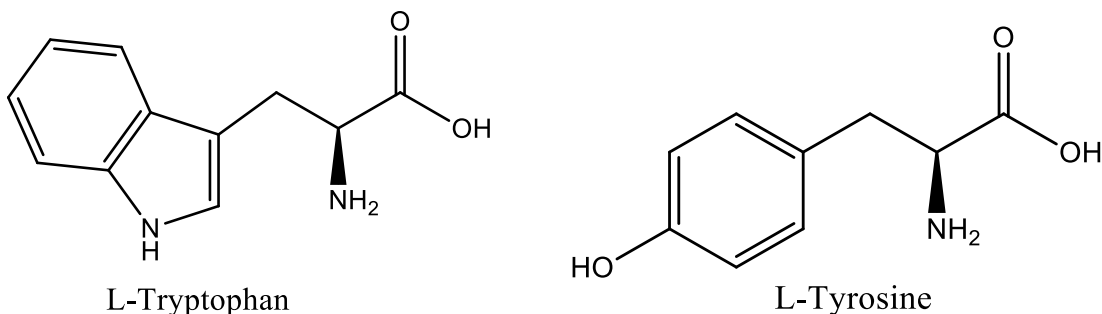
Kopylovich et al., [98] developed a copper-selective PVC membrane electrode using 1-phenyl-2-(2-hydroxyphenylhydrazo)butane-1,3-dione as an ionophore. Fabricated electrode displayed a detection limit of 6.3×10^{-7} M for Cu^{2+} ions at pH 4.0 with response time of 10 s. Sensor was found to have good discriminating ability towards Cu(II) ions over a wide variety of alkali, alkaline earth and transition metal ions. It was successfully applied for the direct determination of copper (II) in zinc, aluminum and nickel-based alloys, in soils polluted by oil and as an indicator electrode for potentiometric titration of copper ions with EDTA.



2-hydroxyphenylhydrazo based Cu(II) selective ionophore[98]

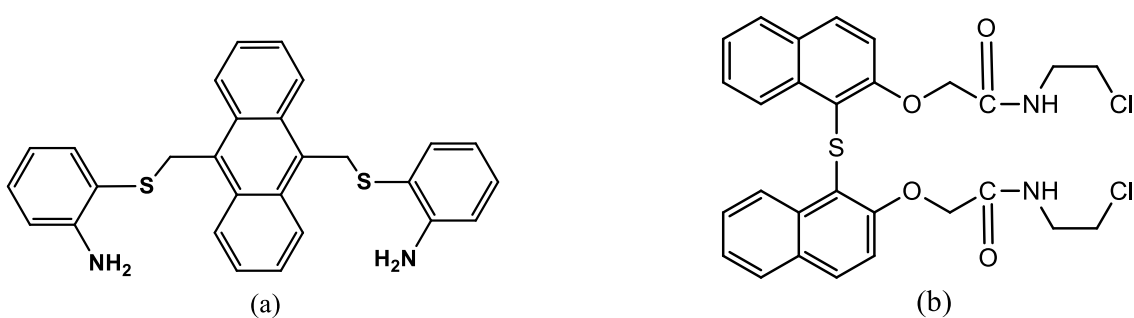
Amino acids L-Tryptophan and L-Tyrosine were developed as Cu^{2+} -selective polymeric membrane electrodes by Kawakami et al., [99]. The proposed ISEs showed rapid Nernstian

responses for the Cu^{2+} ion. Slopes of 30.3 and 29.7mV/decade were observed for L-Tryptophan and L-Tyrosine electrodes, respectively. Both the electrodes exhibited good selectivity with respect to alkaline, alkaline earth, some transition and heavy metal ions as well as the ammonium ion.

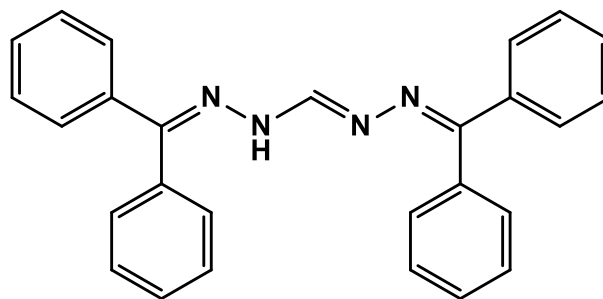


Amino acids as Cu(II) selective ionophores [99]

Quick determination of trace quantities of Ag^+ ion is of critical importance due to its multi-purpose nature and its widespread use in dentistry, electronic and photographic film production industry. Mittal et al., [100] used 9,10, Bis-(2-aminophenylthio)methylene anthracene as ionophore for fabricating a liquid membrane electrode for Ag(I) determination. The potentiometric sensor displayed a linear response towards Ag^+ ions with a slope of 60 mV/decade and a detection limit of $3 \times 10^{-5}\text{M}$. The electrode showed a good response to silver ions in the presence of mercury ions. The electrode worked well in mixed solvent media also.



fabricated. The electrode exhibited linear response with a detection limit of 8.6×10^{-8} M and a response time of less than 10 s. Due to its high selectivity for Ag(I) ions, it was used as an indicator electrode for indirect determination of vitamin B1 in tablets by determination of Cl^- ions in this compound with a standard solution of AgNO_3 . Seo et al., [102] reported a Schiff base N,N-bis(pyridin-2-ylmethylene)benzene-1,2-diamine as ionophore for preparing PVC based membrane sensors selective to silver ions. The sensor displayed good selectivity to silver ion over a number of competitive ions. Hassouna et al., [103] prepared a silver (I)-selective electrode by incorporating N,N-bis(3-methyl-1-phenyl-4-benzylidene-5-pyrazolone)propylenediamine as a neutral ionophore into plasticized PVC membranes. Excellent selectivity towards Ag^+ ions over alkali, alkaline earth, and transition metals ions was noticed. Density Functional Theory calculations performed using the Gaussian 03 program indicated a tetradentate coordination of the metal ion by ionophore. Electrode was successfully used in the potentiometric titration of halides with silver ion and in the determination of silver in radiology films. Dadkhah et al., [104] reported an Ag(I)-selective electrode based on a newly synthesized N,N-bis(benzophenone imine)formamidine Schiff base as an ionophore. The electrode displayed a perfect Nernstian response to Ag^+ ions with a detection limit of 5.0×10^{-8} M over a wide pH range of 2.0–9.0. Spectrophotometric studies exhibited a 1:1 stoichiometry of the Ag^+ –Ionophore complex in methanol solution. Electrode demonstrated good selectivity towards Ag^+ ion in comparison to alkali, alkaline earth, transition and heavy metal ions.

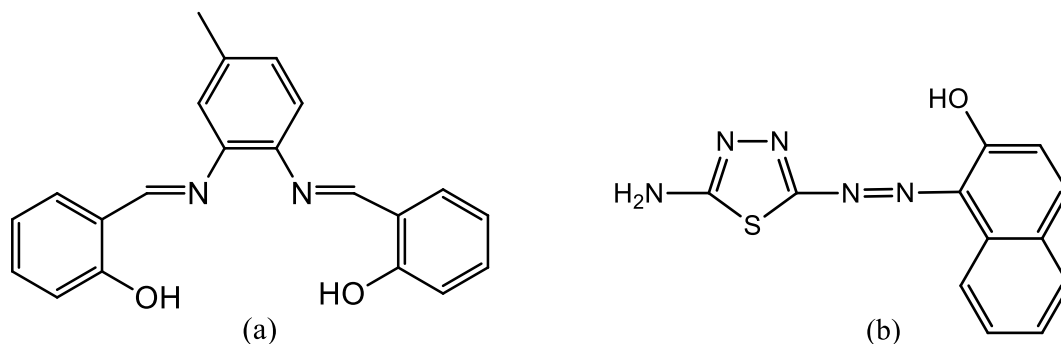


Schiff base based Ag (I) selective ionophore [104]

Mn(II) is another biologically important metal ion. Mashhadizadeh et al., [105] reported a Mn(II)-selective PVC membrane electrode using 5-[(4-nitrophenylazo)-N-hexylamine]salicylaldimine as an ionophore. A slope of 30.1 mV/decade over a concentration

range 4.0×10^{-7} to 1.8×10^{-2} M with a detection limit of 1.0×10^{-7} M was observed. It was used as an indicator electrode in potentiometric titration of Mn^{2+} ions with EDTA solution. Another Mn^{2+} -selective sensor based on 3-((6-aminopyridin-2-ylimino)-1,3-diphenylpropylidene)pyridine-2,6-diamine was reported by Gupta et al., [106]. The sensor displayed a working concentration range of 1×10^{-6} to 1×10^{-1} M. The selectivity coefficients determined by matched potential method (MPM) and fixed interference method (FIM) indicated high selectivity for Mn^{2+} . The sensor was successfully used in determination of Mn(II) ions in spiked water samples and in some natural plant and edible species. A Mn^{2+} potentiometric membrane sensor was developed by Kumar et al., [107] using 2,8,14,20-tetrakis(naphthyl)calix[4]resorcinarene as an ionophore. A Nernstian response along with a detection limit of 5.1×10^{-6} M was observed. The electrode was successfully applied for the potentiometric titration of Mn (II) against EDTA.

Co^{2+} -selective PVC membrane electrode based on N,N-bis(salicylidene)-3,4-diaminotoluene was reported by Gupta et al., [108]. Sensor exhibited a linear potential response in the concentration range of 7.9×10^{-8} to 1.0×10^{-1} M with a slope of 30 mV/decade. Electrode was successfully applied for the determination of Co^{2+} ions in real samples.

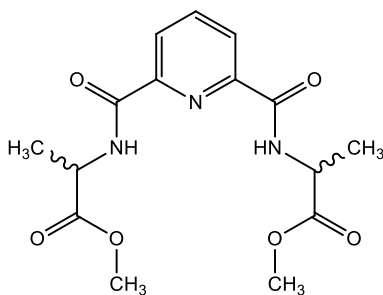


Co (II) selective ionophores based on (a) Schiff base [108] and (b) Thiadiazole derivative [109]

Wardak, [109] reported Co^{2+} -selective potentiometric sensor based on 2-amino-5-(hydroxynaphtyloazo-1')-1,3,4 thiadiazole. The electrode displayed a low detection limit of 1.5×10^{-6} M. Kumar et al., [110] reported a cobalt(II)-selective PVC membrane sensor using *p*-(4-*n*-butylphenylazo)calix[4]arene as an ionophore along with sodium tetraphenylborate and dibutyl(butyl)phosphonate in the ratio 10:100:1:200. Sensor displayed a detection limit

of 4.0×10^{-6} M with a working concentration range of 9.2×10^{-6} to 1.0×10^{-1} M and a slope of 29 mV/decade.

Mahmoud, [111] reported a Fe(II) selective sensor using a plasticized carboxylated poly(vinyl chloride) matrix membrane based on 2,4,6-tri(2-pyridyl)-1,3,5-triazine (TPTZ). Sensor displayed a slope of 32.7 mV/decade and a detection limit of 5.0×10^{-8} M. The constructed sensor was used as indicator electrode in potentiometric titration of $[\text{Fe}(\text{TPTZ})_2]^{2+}$ with tetraphenylborate solution in standard and various pharmaceutical forms. Farahani et al., [112] fabricated Fe^{2+} ISE from polyvinyl chloride matrix membrane containing tetra phenyl porphyrin as an ionophore. The best performance was obtained with the sensor having a membrane of composition of TPP: NaTPB: DBP: PVC in the ratio 6:3:61:30, respectively. The sensor showed a linear response over a wide concentration range of 1.0×10^{-6} to 1.0×10^{-2} M with a Nemstian slope of 29.4 ± 0.6 mV/ decade and a detection limit of 9.6×10^{-7} M. N-phenylaza-15-crown-5 was used as an ionophore by Aghaie et al., [113] to develop a PVC membrane Fe(II)-selective electrode, which displayed a Nernstian slope of 29.2 mV/decade over a concentration range of 1.0×10^{-6} to 1.0×10^{-2} M. The electrode can be used in ethanol and dioxane media up to 20% and 5% (v/v) concentration, respectively, without interference. The electrode was used for direct determination of Fe^{2+} in the ferrous sulfate syrup. Abounassif et al., [114] reported the use of chiral 2,6-bis-(carboxamidemethylester)pyridine derivative to prepare Fe(II)-selective PVC membrane sensor. The sensor displayed a near-Nernstian response with a slope of 31.5 mV/decade. The sensor showed high selectivity for Fe^{2+} over Fe^{3+} ions and a number of transition, alkaline earth and alkali metal ions. The sensor was successfully applied for the measurement of ferrous ions in drug formulations.

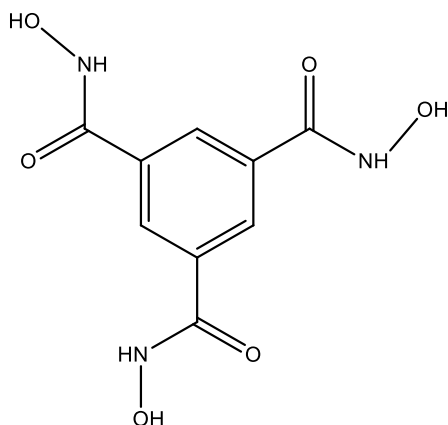


Ag (I) selective ionophore based on carboxamide methylester derivative of pyridine [114]

Agilan et al., [115] proposed two ferrous-selective modified carbon paste electrodes based on 5,5'-(propane-1,3-diyl-bis(sulfanediyl))bis(3-benzyl-4H-1,2,4-triazol-4-amine) (I) and 5,5'-(butane-1,4-diyl-bis(sulfanediyl))bis(3-benzyl-4H-1,2,4-triazol-4-amine) (II) as ionophores. The electrodes displayed slopes of 30.2 and 29.1 mV/decade for electrode (I) and (II), respectively. Both the electrodes showed linear response with a detection limit of 1.0×10^{-7} M for Fe(II) ions. The proposed sensors were successfully applied for the determination of Fe(II) ions in different real-life samples. Gholami et al., [116] proposed a polypyrrole based Fe(II)-selective carbon screen-printed electrode as a potentiometric and voltammetric sensor. The potentiometric dynamic range was 1.0×10^{-6} to 1.0×10^{-1} M with a Nernstian slope of 29.7 ± 0.5 mV per decade. The prepared electrode had good potentiometric selectivity for Iron II with respect to several cations. Sensor was successfully used for the potentiometric determination of Fe(II) concentration in ferrous fumarate tablet.

2.3.2 Spectrophotometric sensors

The design and synthesis of spectrophotometric sensors for detection of transition metal ions in aqueous and nonaqueous media is a fascinating field and has developed a lot in the last decade. These sensors are able to bind selectively and reversibly the species of interest with a change in the sensing system property, such as absorption and emission, which may allow naked eye detection of the target species without using any costly instruments. Spectrophotometric sensors present many advantages. These are usually very sensitive, low cost, and versatile [117]. We are reporting a few important developments in this field. A tripodal sensor based on Benzene-1,3,5-tricarbonylhydroxamate (BTHA) was reported as a pH sensitive colorimetric sensor for Fe^{3+} ions by Baral et al., [118]. Spectrophotometric, potentiometric and theoretical investigations revealed a 3:1 metal ligand stoichiometry in a highly aqueous medium (9:1 H_2O : DMSO). Formation constant values of 28.73, 26.13 and 19.69 calculated for three metal ions Fe^{3+} , Al^{3+} and Cr^{3+} respectively indicated a strong affinity of sensor towards Fe^{3+} ions. A substantial shifting in both of the peaks (at 238 nm and 270 nm) in presence of the metal ions indicated a strong coordination between ligand and Fe^{3+} ions. Moreover, complexation of BTHA with iron shows three distinct colors, violet, reddish orange and yellow at different pH.



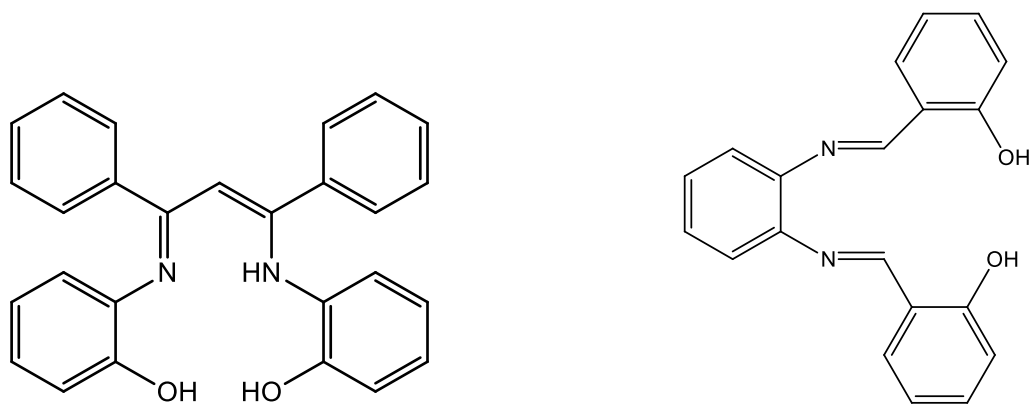
Tripodal ionophore selective for Fe (III) [118]

Modi et al., [119] used pyrazolones as Fe(III)-selective fluorescence sensor. Fluorescence properties of five 4-acyl pyrazolone based hydrazides and their Fe (III) heterochelates in the solution state were done. The fluorescence spectra of heterochelates showed red shift, which may be due to the complexation by the ligands to the ferric ion. It enhances ligand's ability to accept electrons and decreases the electron transition energy. A highly selective ferric ion sensor based on a naphthalimide derivative was reported by Xu et al., [120]. The sensor displayed rapid response and high selectivity for the determination of Fe^{3+} ions in aqueous media. The proposed sensor exhibited a linear response towards Fe^{3+} ions in the concentration range covering from 1.0×10^{-5} to 1.0×10^{-3} M and a detection limit of 4.5×10^{-6} M.

Tumer et al., [121] reported naked eye detection of Hg(II) ion using *N, N'*-bis(3,4,5-trimethoxy phenylidene)-1,5-diamino naphthalene as an optical sensor. The sensor properties were examined and a bathochromic shift from 545 to 585 nm was observed resulting in a colour change upon addition of the metal cations, such as Hg(II), Cu(II), Co(II) and Al(III). As observed, the compound showed higher selectivity towards the softer cation Hg(II), as compared to the harder cations K(I), Na(I), Ba(II), Cd(II), Co(II), Cu(II), Mg(II), Mn(II), Ni(II), Zn(II) and Al(III) in day light. Addition of Hg^{2+} ions changed the colourless solutions to yellowish tinge. A highly selective and sensitive colorimetric and fluorogenic sensor (L_1) for $\text{Hg}^{2+}/\text{Cr}^{3+}$ was reported by Das et al., [122]. Binding of L_1 to the Hg^{2+} or Cr^{3+} generated a new intense absorption band at 509 nm resulting in a visually detectable colour change from yellow to red. Importantly, the sensor showed specific binding to Cr^{3+} in the presence of an excess of iodide ions, which acted as a masking agent for Hg^{2+} .

Gupta et al., [123] reported a colorimetric chemosensor based on Schiff's moiety for Cu^{2+} ions. It exhibited highly selective and sensitive recognition towards Cu(II) ion over other metal ions in a wide pH range. The complex formed between the ligand and Cu^{2+} ion was found to have 1:1 stoichiometry with an association constant of $1.0 \times 10^6 \text{ M}^{-1}$. The chemosensor exhibited a colour change from colourless to yellowish brown upon complexation with copper ions, which can be reversed by adding EDTA as restoring agent.

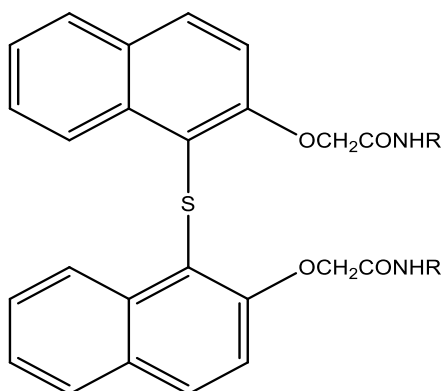
Kim, [124] recently reported the spectrophotometric behaviour of diazophenylcalix[4]arene bearing *para*-ethylester group (p-EAC). Absorption spectra of p-EAC exhibited decrease in absorbance at 353 nm in the presence of Cr^{3+} , Fe^{2+} , Pb^{2+} , and Cu^{2+} ions. While Cr^{3+} , Fe^{2+} and Pb^{2+} ions induced a bathochromic shift in absorption maximum with decreasing order of absorbance ($\text{Cr}^{3+} > \text{Fe}^{2+} > \text{Pb}^{2+}$), a hypsochromic shift was observed on the addition of Cu^{2+} . This resulted in the selective colouration from light green to orange and colorless for Cr^{3+} and Cu^{2+} that can be detected by the naked eye, respectively. N, N'-bis(salicylidene)-o-phenylenediamine was reported as a Cu(II) selective chemosensor by Fang et al., [125]. The fluorescence of proposed receptor was quenched by addition of Cu^{2+} at pH 8.2, whereas it is nearly unaffected by other metal ions. Under the optimum conditions, a good linear relation was observed between the quenching efficiency (F_0/F) and the concentration of Cu^{2+} in the range of 1.0×10^{-7} – $2.5 \times 10^{-6} \text{ mol L}^{-1}$. The detection limit (3σ) for Cu^{2+} determination is $2.0 \times 10^{-8} \text{ M}$. Sensor was successfully used for quantification of Cu^{2+} in soybean milk powder.



Cu (II) selective ionophores based on Schiff bases [123] and [125]

Kandasamy et al., [126] explored the chemosensing properties of a coumarin molecule 4-hydroxy-3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(1,3-diphenyl-1H-pyrazol-4-yl)methyl)-2H-chromen-2-one (PBC) towards transition metal ions. The PBC solution with Cu^{2+} and Zn^{2+} ion showed brown and blue colour, respectively. Further, the Job's plot method confirmed the 1:1 and 2:1 stoichiometry of the complex formation between the PBC with Cu^{2+} and Zn^{2+} ions, respectively. Zhang et al., [127] reported a colorimetric probe 3-bromo-5-methylsalicylaldehyde rhodamine B hydrazone (BMSRH) for Cu^{2+} ions. Addition of Cu^{2+} to the solution of BMSRH resulted in a colour change from colourless to red together with a new band appeared at 552 nm in the UV-vis absorption spectra. Studies indicated a 1:1 stoichiometry between BMSRH and Cu^{2+} ions with an association constant of $3.2 \times 10^4 \text{ L mol}^{-1}$. A linear dynamic range of 0.667–240 $\mu\text{mol/L}$ was observed.

Wang et al., [128] reported a Ni^{2+} chemosensor using a coumarin Schiff base in acetonitrile medium. Addition of Ni^{2+} to CH_3CN solution of Ligand resulted in a rapid color change from yellow to red together with a large red shift from 465 to 516 nm. Other common alkali, alkaline earth, transition and rare earth metal ions induced no or minimal spectral changes. Experimental results indicated that proposed Schiff base could be used as a potential Ni^{2+} colorimetric and naked-eye chemosensor in CH_3CN solution. Han et al., [129] reported a Nickel selective colorimetric sensor based on pyrazoline. The addition of Ni^{2+} to ethanol solution of the synthesized pyrazoline resulted in a rapid color change from blue to green which allows the selective detection of Ni^{2+} ion over a great number of other metal ions. The association constant for the 1:1 complex was determined to be $2.72 \times 10^7 \text{ M}^{-1}$.



Dinaphthosulfide based podand selective for transition metal ions [130]

Shockravi et al., [130] used a dinaphthosulfide podand for spectrophotometric determination of trace amount of Ag^+ , Hg^{2+} , Cr^{3+} , Pb^{2+} , and Ni^{2+} cations. Formation constants of different 1:1 metal complexes were determined from the absorbance-mole ratio data and found to vary in the order $\text{Pb}^{2+} > \text{Ni}^{2+} > \text{Hg}^{2+} > \text{Cr}^{3+} > \text{Ag}^+$ indicating strongest affinity towards Pb^{2+} ions.

2.4 References

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METHODOLOGY

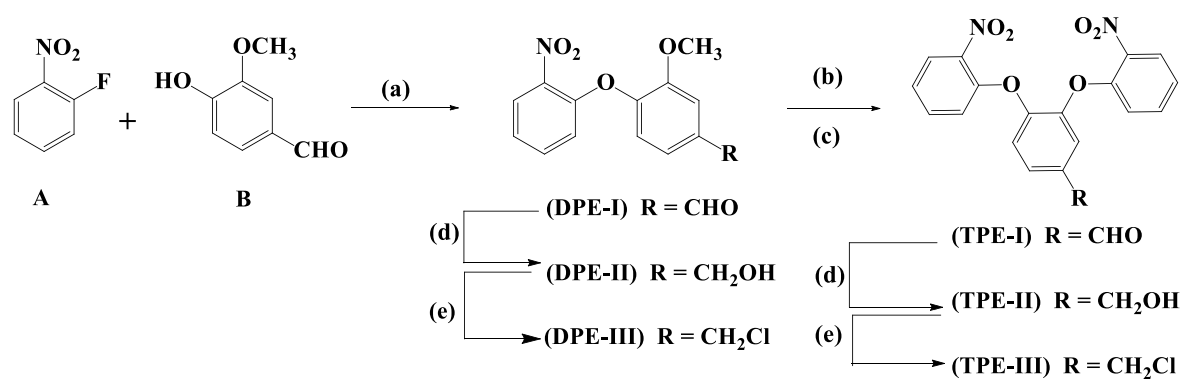
The design and synthesis of ionic recognition materials are subjects of continuous interest due to their widespread applications in environmental, agricultural, clinical and industrial investigations. In the last four decades many cyclic and acyclic recognition compounds, which can be categorized as crowns, calixarenes, cryptands and podands have been reported. These recognition compounds found their use in various types of analytical methods such as spectroscopic, electrochemical, inductively coupled plasma, atomic absorption spectrometry (AAS) etc. to detect different metal ions in trace amounts with high selectivity. The selectivity in the cyclic ones could be attributed to a cavity due to their rigid structure and in the acyclic ones to their end groups, which may either reorient themselves to form a pseudo cavity in the presence of an ion or may provide rigidity to their otherwise flexible structure. Though the oxygen containing ring systems like crownethers and other macrocycle based sensors are well known as good ligands for metal ions, the corresponding acyclic ether based sensors are comparatively lesser [1-7] known. Most of these acyclic receptors have a rigid-flexible-rigid type arrangement in which the flexible part was constituted of oxygen atoms separated by aliphatic units, usually containing two carbon atoms. Due to their flexibility, such receptors can usually orient themselves in a way so as to best fit the metal ion.

Keeping in view the required delicate balance of “rigidity” (for high selectivity) and “flexibility” (for a sufficiently fast ion exchange) of a sensor molecule, it was interesting to explore the ionophoric potential of acyclic arylethers and their aza analogues, which have phenyl units for the required rigidity and as a whole the unit is having reasonable flexibility.

Further, this property of arylether and arylamine linkage can be used in potentiometric ion selective electrodes, which offer the advantage over other analytical techniques in terms of sensitivity, selectivity, fast response, cost and convenience.

Thus, six acyclic arylethers and two acyclic arylamines were prepared, as shown in scheme 3.1 and scheme 3.2 and their potentiometric studies were carried out. The presence of various substituents from remote, or near to the oxygen / nitrogen atom of ether / amine linkage could

result in different types of complex formation with alkaline earth and transition metal ions. The proposed ionophores have the advantages of easy synthesis and purification. Also, a dramatic change in their selectivity and sensitivity is observed upon making different steric and electronic variations in their structures. Various experimental conditions like the composition of membrane ingredients, suitable concentration of the internal solution of the electrode have been optimized to obtain a better working concentration range, detection limit and other response characteristics.



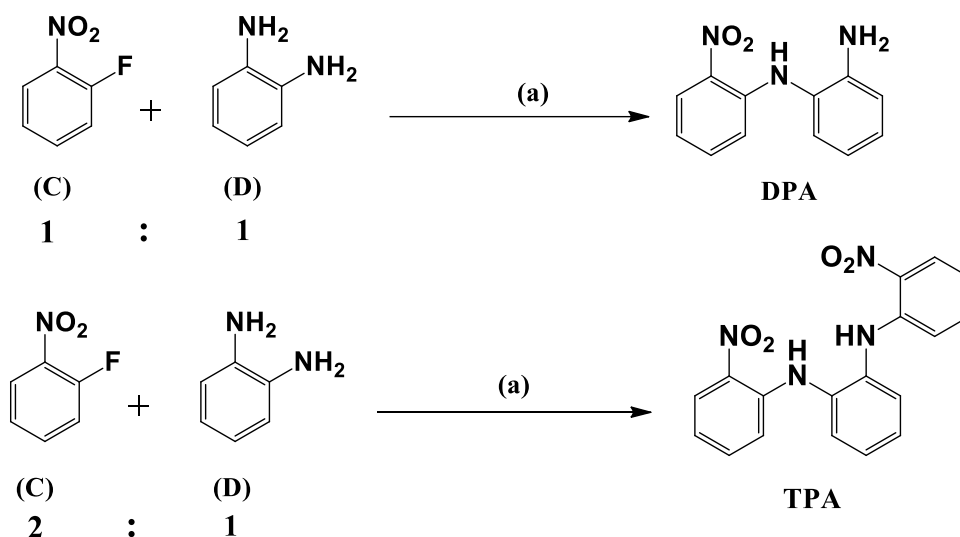
Reagents : (a) K₂CO₃, 18-Crown-6, DMF, RT (b) 48% Aq. HBr, CH₃COOH, 120°C, (c) A, K₂CO₃, 18-Crown-6, DMF, 100°C (d) NaBH₄, MeOH (e) MsCl, Et₃N, DCM, RT

Scheme 3.1 Synthesis of Arylether Ionophores

3.1 Materials and Instrumentation

All reagents used in synthesis were purchased from reputed suppliers like LOBA Chemie (India), Sd Fine (India) and others and used without further purification. Solvents were distilled before doing the column chromatography. TLC analysis was performed on silica gel plates and column chromatography was conducted over silica gel (mesh 100 – 120). The UV-Vis spectra were recorded on Analytic Jena (Specord 200 UV – Visible) double beam spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on 400.1 and 100.6 MHz spectrometer [Avance - II(Bruker)] with CDCl₃ and tetramethylsilane as the internal standard (δ, ppm) respectively. Mass spectra were recorded on Waters Micromass Q – Tof (LC-MS) spectrograph. High molecular weight polyvinylchloride (PVC), o-nitrophenyloctylether (o-

NPOE) and sodium tetraphenylborate, tetrahydrofuran (THF) were purchased from Aldrich (India) and used as received. Metal salt solutions of concentration 0.1M were prepared by dissolving AR grade metal salts in double distilled water and standardized wherever necessary. Working solutions of different concentrations were prepared by serial dilutions. Potentials were measured with an Equip-Tronics (EQ-602, accuracy, $\pm 0.1\text{mV}$) potentiometer (Mumbai, India).



Reagents : (a) K_2CO_3 , CuI, Proline, DMSO, 110°C , 24 hrs

Scheme 3.2 Synthesis of Arylamine Ionophores

3.2 Synthesis and characterization of ionophores

3-methoxy-4-(2-nitrophenoxy) benzaldehyde (DPE-I)

To a solution of 1-fluoro-2-nitrobenzene (1.88 mL, 17.8 mmol) taken in DMF (25 mL) were added K_2CO_3 (9.9 g, 71.7mmol), 3-methoxy-4-hydroxybenzaldehyde (3.0 g, 19.7 mmol), and 18-crown-6 (50 mg, 0.2mmol). The mixture was stirred at room temperature for 12 hours. After the reaction was complete (monitored with TLC), the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with water (50 mL), NaOH (1N, 3×10 mL), water (until neutral to litmus paper), brine, and dried over Na_2SO_4 . Evaporation of the organic solvent gave product which was purified using SiO_2 column chromatography and solvent (petroleum ether /ethyl acetate = 70:30) to afford a yellow solid **DPE-I** in 86.5 % (4.2 g) yield. ^1H NMR (400MHz ,

CDCl₃) ; δ = 9.9 (s,1H), 7.9 - 8.0 (d,1H, J = 6.4 Hz), 7.54 – 7.58 (m, 2H), 7.45 – 7.47 (d,1H, J = 6 Hz), 7.25 – 7.30 (t, 1H, J=7.2 Hz), 7.05 – 7.07 (d, 1H, J = 8 Hz), 6.99 – 7.01 (d, 1H, J = 7.2 Hz), 3.89 (s, 3H). ¹³C NMR (100.6 MHz, CDCl₃); δ 190.8, 151.1, 149.74, 149.7, 140.84, 134.5, 133.6, 125.9, 125.3, 124, 124.4, 120.4, 119.4, 111.3, 56.18. MS: m/z 272.3 [M⁺-1]; calculated [M⁺-1]; for C₁₄H₁₁O₅N: 272 (Figures 3.1, 3.2 & 3.3)

3-methoxy-4-(2-nitrophenoxy) benzylalcohol (DPE-II)

To an ice cold suspension of **DPE-I** (500 mg, 1.8 mmol) in methanol (30 mL), sodium borohydride (83.5 mg, 2 mmol) was added slowly over a period of 20 minutes. The reaction mixture was stirred at room temperature for about half an hour. After the reaction was complete (monitored with TLC), solvent was evaporated in vacuum and reaction quenched with water. It was extracted with ethylacetate and washed with water and dried over Na₂SO₄. Evaporation of the solvent gave product which was purified using SiO₂ column chromatography and solvent (petroleum ether /ethyl acetate = 50:50) to afford a yellow solid **DPE-II** in 65 % (321mg) yield. ¹H NMR (400MHz , CDCl₃) ; δ = 7.9 (d,1H, J=6.4 Hz), 7.4 (t,1H, J = 5.6 Hz), 7.1(m, 1H), 7.05 (m,1H), 6.9 (d, 1H, J=6 Hz), 6.8 (d, 1H, J = 7.2 Hz), 4.6 (s,2H), 3.7(s,3H), 2.1(s,1H). ¹³CNMR (100.6 MHz, CDCl₃); δ 151.69, 151.30, 142.54, 139.93, 139.44, 134.13, 125.67, 122.15, 121.62, 119.49, 118.15, 111.79, 64.74, 55.99. MS: m/z 298 [M + Na]⁺; calculated [M + Na]⁺ for C₁₄H₁₃O₅N: 298. (Figures 3.4, 3.5 & 3.6)

3-methoxy-4-(2-nitrophenoxy) benzylchloride (DPE-III)

3-methoxy-4-(2-nitrophenoxy) benzylalcohol (**DPE-II**) (500mg, 1.8 mmol) was dissolved in dry dichloro methane(25 mL). The resulting solution was cooled to 0 °C in an ice-bath. Triethylamine (506 μ L, 3.6 mmol) and methane sulphonyl chloride (281 μ L, 3.6 mmol) were added to the reaction mixture and stirred at room temperature for 20 hours. After the reaction was complete (monitored with TLC), the reaction mixture was diluted with dichloromethane (20mL) and the organic layer washed with water and dried over Na₂SO₄. Evaporation of the solvent gave product which was purified using SiO₂ column chromatography and solvent (petroleum ether /ethyl acetate = 50:50) to afford a yellow solid **DPE-III** in 76 % (403 mg) yield. ¹H NMR (400MHz, CDCl₃) ; δ = 7.9 (m,1H), 7.7 (d, 2H, J = 1.6 Hz), 7.5(m, 1H), 7.4 (s, 1H), 7.0 (d, 1H, J=8.0 Hz), 6.9 (d, 1H, J = 8.0 Hz), 4.7 (s, 2H), 3.8(s, 3H). ¹³CNMR (100.6

MHz, CDCl₃); δ 155.3, 151.63, 146.44, 141.76, 138.80, 135.68, 128.78, 125.29, 122.72, 122.20, 117.86, 111.77, 65.39, 56.29. (Figures 3.7 & 3.8)

3,4-bis (2-nitrophenoxy) benzaldehyde (TPE-I)

Compound **DPE-I** (400 mg, 1.46 mmol) obtained above was taken in acetic acid (20 mL) and HBr (48% aqueous, 2 mL). The mixture was heated under reflux for 4 hours. After cooling to room temperature and confirming completion of the reaction (TLC monitoring), acetic acid was evaporated under vacuum. To the dried viscous mass was added water (5mL) and NaOH (1N, 2.5mL) to convert phenol into its corresponding sodium salt. This was treated with ethyl acetate (3×10 mL) to remove any organic starting material. The aqueous layer obtained, containing pure salt of corresponding phenol, was acidified with dil HCl to pH 2. The aqueous layer was again extracted with ethyl acetate (3×10 mL), washed with water (until neutral to litmus paper) and dried over Na₂SO₄. Evaporation of organic solvent gave yellow solid.

The yellow solid (500 mg) obtained above was taken in DMF (10 mL) and 1-fluoro-2-nitrobenzene (284 μ L, 2.6 mmol), K₂CO₃ (1.06 g, 7.68 mmol) and 18-crown-6 (20 mg, 0.075 mmol) added. The mixture was heated under reflux (100°C) for 12 hours. After the reaction was complete (monitored with TLC), the reaction mixture was diluted with CH₂Cl₂ (20 mL), washed with water (20 mL), NaOH (1N, 2×10 mL), water (until neutral to litmus paper), brine, and dried over Na₂SO₄. Evaporation of the organic solvent gave product which was purified using SiO₂ column chromatography and solvent (petroleum ether/ethyl acetate = 70:30) to afford a brown solid (**TPE-I**) in 65% (470 mg) yield. ¹H NMR (400MHz, CDCl₃); δ = 9.9 (s, 1H), 7.9 – 8.0 (t, 2H, J = 6.76 Hz), 7.6 – 7.7 (d, 1H, J = 6.48Hz), 7.56 – 7.64 (m, 3H), 7.31 – 7.35 (t, 1H, J = 4 Hz), 7.25 – 7.29 (t, 1H, J = 6.4 Hz), 7.09 – 7.18 (m, 3H). ¹³C NMR (100.6 MHz, CDCl₃); δ 189.8, 152.0, 149.3, 148.4, 146.6, 141.1, 140.7, 134.9, 134.7, 133.4, 128.1, 126.04, 126.0, 125.1, 124.3, 121.7, 120.6, 120.4, 119.6. MS: m/z 403.3 [M + Na]⁺; calculated [M + Na]⁺ for C₁₉H₁₂O₇N₂: 403. (Figures 3.9, 3.10 & 3.11)

3,4-bis (2-nitrophenoxy)benzylalcohol (TPE-II)

To an ice cold suspension of **TPE-I** (2g, 5.2 mmol) in methanol (50 mL), sodium borohydride (240 mg, 6.31 mmol) was added slowly over a period of 30 minutes. The reaction mixture was stirred at room temperature for about an hour. After the reaction was complete (monitored with TLC), solvent was evaporated in vacuum and reaction quenched with water. It was

extracted with ethyl acetate and washed with water and dried over Na₂SO₄. Evaporation of the solvent gave product which was purified using SiO₂ column chromatography and solvent (petroleum ether /ethyl acetate = 50:50) to afford a yellow solid **TPE-II** in 63 % (1.24g) yield. ¹H NMR (400 MHz, CDCl₃); δ = 7.8 (d, 2H, J=6.1Hz), 7.4 – 7.5 (t, 2H, J = 3.6 Hz), 7.22 – 7.27 (m, 1H), 7.13 – 7.20 (m, 4H), 6.9 (t, 2H, J = 7.2 Hz), 4.6 (s, 2H), 2.1 (s, 1H). ¹³C NMR (100.6 MHz, CDCl₃); δ 150.3, 150.1, 145.9, 144.9, 140.0, 139.9, 139.7, 134.49, 134.45, 125.7, 124.4, 123.3, 123.2, 122.2, 120.3, 119.1, 118.9, 64.0. MS: m/z 405.3 [M + Na]⁺; calculated [M + Na]⁺ for C₁₉H₁₄O₇N₂: 405. (Figures 3.12, 3.13 & 3.14)

3,4-bis (2-nitrophenoxy)benzylchloride (TPE-III)

3,4-bis(2-nitrophenoxy)benzylalcohol (**TPE-II**) (500mg, 1.3 mmol) was dissolved in dry dichloro methane (25 mL). The resulting solution was cooled to 0 °C in an ice-bath. Methane sulphonyl chloride (202 μL, 2.6 mmol) and triethylamine (364 μL, 2.6 mmol) were added to the reaction mixture and stirred at room temperature for 20 hours. After the reaction was complete (monitored with TLC), the reaction mixture was diluted with dichloromethane (20mL) and the organic layer washed with water and dried over Na₂SO₄. Evaporation of the solvent gave product which was purified using SiO₂ column chromatography and solvent (petroleum ether /ethyl acetate = 50:50) to afford a yellowish brown solid **TPE-III** in 80 % (416 mg) yield. ¹H NMR (400MHz, CDCl₃); δ = 7.8 (d, 2H, J=3.6Hz), 7.4 – 7.5 (t, 2H, J = 3.2 Hz), 7.26 – 7.28 (m, 1H), 7.12 – 7.22 (m, 4H), 6.9 (d, 2H, J = 7.2 Hz), 4.5 (s, 2H). ¹³C NMR (100.6 MHz, CDCl₃); δ 149.8, 146.0, 145.8, 140.2, 140.1, 135.8, 134.4, 132.3, 130.9, 128.8, 126.3, 125.76, 125.74, 23.6, 123.5, 122.1, 121.9, 119.3, 44.9. MS: m/z 423.3 [M + Na]⁺; calculated [M + Na]⁺ for C₁₉H₁₃O₆N₂Cl: 423.5. (Figures 3.15, 3.16 & 3.17)

N-(2-nitrophenyl)benzene-1,2-diamine (DPA)

To a solution of 1-fluoro-2-nitrobenzene (7.5 mmol, 731.6 μL) in DMSO (5 mL) was added benzene-1,2-diamine (5 mmol, 500 mg), potassium carbonate (10 mmol, 1.27 g), cuprous iodide (0.5 mmol, 88 mg) and L-proline (1.0 mmol, 106 mg). The reaction mixture was heated under reflux at 110 °C for 24 hours. After the completion of the reaction (TLC monitoring), reaction mixture was allowed to cool. It was diluted with ethyl acetate and water. Organic layer was separated and washed with water (until neutral to litmus paper), brine and dried over Na₂SO₄. Evaporation of the organic solvent gave crude product that was purified using SiO₂

column chromatography and solvent (petroleum ether /ethyl acetate = 70:30) to afford a reddish brown solid **DPA** in 71 % (820 mg) yield. ^1H NMR (400MHz, CDCl_3); δ = 7.0 (s, 1H), 6.92 - 6.96 (m, 1H), 6.85 – 6.88 (m, 1H), 6.80 – 6.85 (m, 2H), 6.76– 6.79 (m, 1H), 6.6 (s, 1H), 4.6 (s, 1H), 3.9 (s, 2H). ^{13}C NMR (100.6 MHz, CDCl_3); δ 120.29, 121.11, 123.04, 124.77, 125.12, 126.11, 126.24, 129.88, 130.04, 134.01, 134.85, 134.90. (Figures 3.18 & 3.19)

N, N'-bis(2-nitrophenyl)benzene-1,2-diamine (TPA)

To a solution of 1-fluoro-2-nitrobenzene (12 mmol, 1170 μL) in DMSO (5 mL) was added benzene-1,2-diamine (5.0 mmol, 500 mg), potassium carbonate (20 mmol, 2.5 g), cuprous iodide (1.0 mmol, 176 mg) and L-proline (2.0 mmol, 213 mg). The reaction mixture was heated under reflux at 110 $^\circ\text{C}$ for 30 hours. After the completion of the reaction (TLC monitoring), reaction mixture was allowed to cool. It was diluted with ethyl acetate and water. Organic layer was separated and washed with water (until neutral to litmus paper), brine and dried over Na_2SO_4 . Evaporation of the organic solvent gave crude product that was purified using SiO_2 column chromatography and solvent (petroleum ether /ethyl acetate = 80:20) to afford a brown solid **TPA** in 53 % yield. ^1H NMR (400MHz, CDCl_3); δ = 8.2 (d, 2H, J = 6.8 Hz), 7.85 (m, 2H), 7.75 (m, 1H), 7.6 (q, 2H, J = 7.2 Hz), 7.1 (m, 2H), 6.9 (m, 2H), 4.6 (s, 2H). ^{13}C NMR (100.6 MHz, CDCl_3); δ 113.17, 114.7, 125.84, 126, 126.67, 127.46, 127.90, 127.98, 128.27, 128.75, 129.18, 132.77, 133.48, 135.22, 135.33, 136.31, 136.54, 144.23. (Figures 3.20 & 3.21)

3.3 Spectroscopic studies

Preparation of Solutions

Stock solutions of all the compounds were prepared in acetonitrile: water (8:2 in HEPES buffer at pH 7) medium having concentration $1 \times 10^{-3} \text{ mol L}^{-1}$. Similarly, stock solutions of the metal ions (Na^+ , Co^{2+} , Al^{3+} , Sr^{2+} , K^+ , Cu^{2+} , Ni^{2+} , Zn^{2+} , Ba^{2+} , Mg^{2+} , Fe^{2+} and Ca^{2+}) were made to a concentration of $1 \times 10^{-1} \text{ mol L}^{-1}$. Required concentration was reached at by dilution.

Absorption Studies

Absorption spectra were recorded using quartz cuvette having path length of 1.0 cm. For preliminary studies, binding constant and Job's plot, both receptor and metal salt solutions were mixed in the desired concentrations and the spectra were recorded.

Determination of stability constant (K_a) of Ionophore - M^{2+} complex

The stability constant (K_a) of the ionophore – M^{2+} was determined by the Benesi-Hildebrand equation [8]

$$\frac{1}{\Delta A} = \frac{1}{\Delta A_{Sat.}} + \frac{1}{\Delta A_{Sat.} K_a [M^{n+}]}$$

Where, ΔA is the absorbance difference between the metal complex and the free receptor at a particular wavelength and ΔA_{sat} is the maximum absorbance difference at that wavelength. These values were obtained from the UV – Visible titration data. The stability constant was evaluated graphically by plotting $1/\Delta A$ against $1/[M^{2+}]$ which gave a straight line. K_a value was obtained from the slope and intercept of this straight line.

Determination of the stoichiometry of [Ionophore - M^{2+}] complex

Stoichiometry of the complex was determined by Job's method using following equation and the absorption data obtained as above.

$$\Delta A = |A - (1 - X_M) \cdot A_R^\circ - X_M \cdot A_M^\circ|$$

Where, X_M is the mole fraction of the metal salt, A_R° and A_M° are the absorbances of the solutions of the ionophore and metal salt solutions, respectively. Plot of ΔA verses mole fraction of ionophore gave stoichiometry.

3.4 Potentiometric studies

Preparation of membrane electrode

Membrane components i.e., PVC 28-34%, ionophore 0-7%, ortho – nitrophenyloctylether 59-67% and sodium tetraphenylborate 0-4% were dissolved in 2-3 mL of tetrahydrofuran (THF) [9]. The components were added in terms of weight percentages. The homogenous mixture obtained after complete dissolution of all components was poured in a glass ring of diameter 20 mm placed on dust free glass plate. The homogenous mixture was then allowed to evaporate for 24 h at room temperature. To obtain membranes with similar characteristics, viscosity of the casting solution and the rate of solvent evaporation were controlled so that thickness and morphology of the membranes remain almost unchanged. Transparent membranes so obtained were then removed from the glass ring and circular pieces of 1.25 cm

diameter were cut and glued on the ground end of pyrex glass tube with araldite. Membranes were conditioned with 0.1 M metal salt solutions for 24 hours.

EMF Measurements

The ratio of different membrane ingredients and the contact time were optimized to provide membranes which resulted in reproducible and stable potentials. Also, membranes having only PVC as the membrane ingredients (dummy membranes) were prepared to observe whether any background potentials were produced due to binding material or not. It was observed that potentials were not generated without the ionophore. The activities of metal ions were calculated by using modified form of the Debye-Huckel equation [10]. All emf measurements were carried out with the following assembly:



The concentrations of test solution were varied from 1×10^{-8} M to 1×10^{-1} M. The potential measurements were carried out at 25 ± 0.1 °C with a digital Equip-Tronics potentiometer.

Ion-selective electrodes respond to species according to the Nernst equation, which in turn is dependent upon temperature. Thus, significant measurement errors can occur due to temperature variation. This was taken care of by placing the experimental set up in a thermostat, whose temperature was maintained at 25 ± 0.1 °C. Further, the test solution was thoroughly stirred continuously during the potential measurements with the help of a magnetic stirrer so that a fresh supply of ions to the sensing portion of ISE could be ensured. In order to ensure accuracy of the readings, double distilled water was used to rinse the ISE membranes between measurements. Sufficient time was given for the reading to stabilize. The response time was measured when the potential reading remained stable for about 30 seconds. ISE was kept immersed in standard solution of primary ions when not in use.

Calibration of the electrode

The concentrations of test solution were varied from 1×10^{-8} M to 1×10^{-1} M and their potential values were used to construct a standard calibration curve. Slope, linear range and detection limit are three important parameters of an ISE, which can be calculated from the standard calibration curve. Calibration curve usually exhibits linear response in a range between 10^{-5} M to 10^{-1} M. Slope is calculated from the linear part of the calibration curve and its theoretical value according to Nernst equation is 29.58 mV/ decade for a bivalent ion. The detection limit

is defined according to IUPAC recommendations [11,12] as the cross-section of two extrapolated linear parts of the calibration curve.

Selectivity

Ion-selective electrodes are rarely ion-specific. The ability of an ISE to distinguish between different ions in the same solution is expressed as the selectivity coefficient. The selectivity coefficient depends on various factors like temperature, concentration of both the ions and the total ionic strength of the solution as well as on the method of their determination. Determination of selectivity coefficients can be carried out by different methods that fall into two main groups, namely Mixed solution methods and Separate solution methods. Due to its good mix of realism and simplicity the Fixed Interference Method (FIM), which is a mixed solution method, is the most commonly used approach. The potentiometric selectivity coefficients are expressed according to the Nicolsky – Eisenman equation as

$$E = E_0 + RT / (Z_A F) \ln[a_A + \sum_B K_{A,B}^{pot} (a_B)^{Z_A/Z_B}]$$

Where, E is the measured potential; E_0 is a constant that includes the standard potential of the electrode, the reference electrode potential and the junction potential; z_A and z_B are charges of the primary ion A and of the interfering ion B; a_A and a_B are the activities of the primary ion A and the interfering ion B; K_{AB}^{Pot} is the potentiometric selectivity coefficient for the primary ion A against the interfering ion B. R, T and F have the usual meanings. If $\log K_{AB}^{Pot}$ has positive value, the ISE responds to the interfering ions more selectively than to the primary ions. In most cases, $\log K_{AB}^{Pot}$ has negative value, which means that such ISEs respond to the primary ions more selectively than to the interfering ions. The selectivity coefficients were measured using Fixed Interference Method (FIM).

Fixed Interference Method

The electromotive force (emf) of a cell comprising an ion- selective electrode and a reference electrode is measured for solutions of constant activity of the interfering ion, a_B , and varying activity of the primary ion a_A . The emf values obtained are plotted versus the logarithm of the

activity of the primary ion. The intersection of the extrapolated linear portions of this plot indicates the value of a_A which is to be used to calculate K_{AB}^{Pot} from the following equation:

$$K_{AB}^{Pot} = a_A / (a_B)^{Z_A/Z_B}$$

Where, both z_A and z_B have the same signs, positive or negative.

Determination of formation constants

The selective complexation of ionophore with analyte ions is mainly responsible for the selectivity of the sensors. Sandwich membrane method was used for the potentiometric determination of ionophore-complex formation constants. The sandwich membrane was prepared by pressing together two individual membranes (one without ionophore and one with the same components and an additional ionophore) immediately after blotting them individually dry with tissue paper. The membrane so prepared was fixed on one end of a glass tube with grounded surface and used as electrode for determining the stability constants. The stability constants are then calculated according to the method proposed by Mi and Bakker [13] using following equation:

$$\beta_{IL_n} = \left(L_T - \frac{nR_T}{Z_I} \right)^{-n} \exp \left(\frac{E_M Z_I F}{RT} \right)$$

Where, L_T is the total concentration of ionophore in the membrane segment, R_T is the concentration of lipophilic ionic site additives, n is the ion-ionophore complex stoichiometry, R , T and F have the usual meanings and primary ion carries a charge z_i . E_M i.e., the potential of sandwich membranes was determined by subtracting the cell potential for a membrane without ionophore from that of sandwich membrane for the same system.

3.5 Quantum Chemical Studies

The quantum chemical study was carried out by density functional theory (DFT) method using Gauss View 4.1.2 software. B3LYP method with 6-311G and 6-31G basis sets was employed for optimization, separately for the ionophores and ionophores in presence of metal ions.

3.6 References

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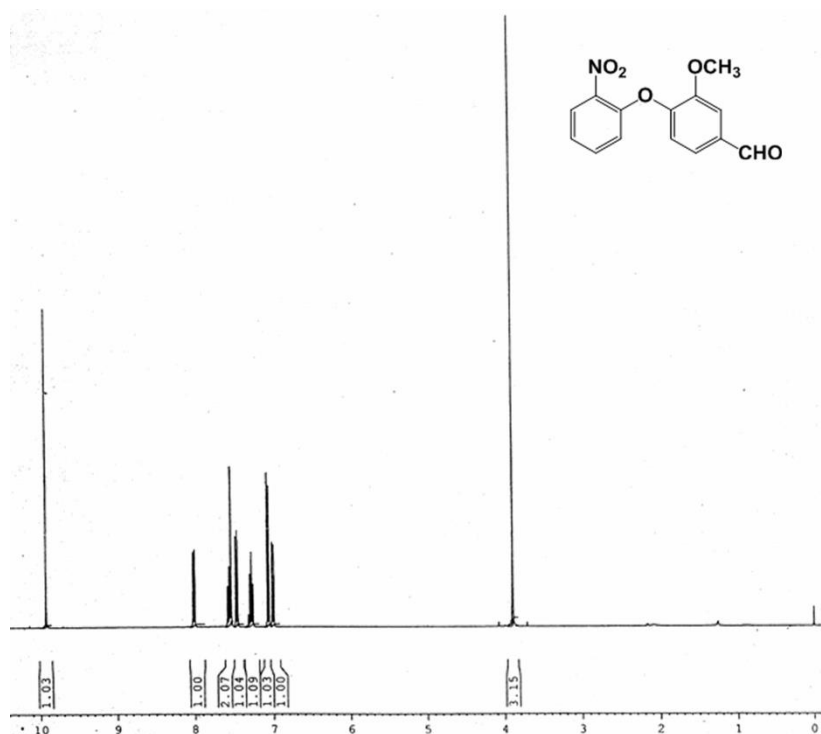


Figure 3.1 ¹H NMR spectrum (400 MHz, CDCl₃) of **DPE-I**

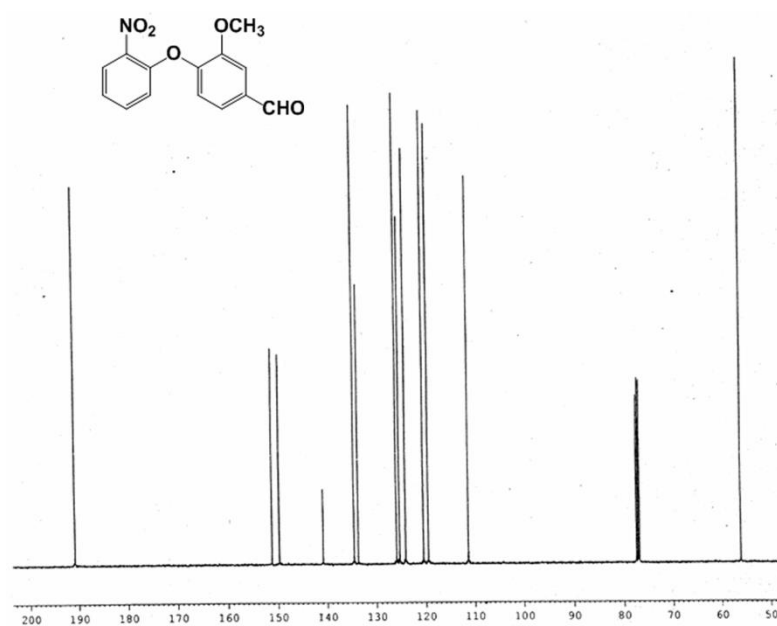


Figure 3.2 ¹³C NMR spectrum (100.6 MHz, CDCl₃) of **DPE-I**

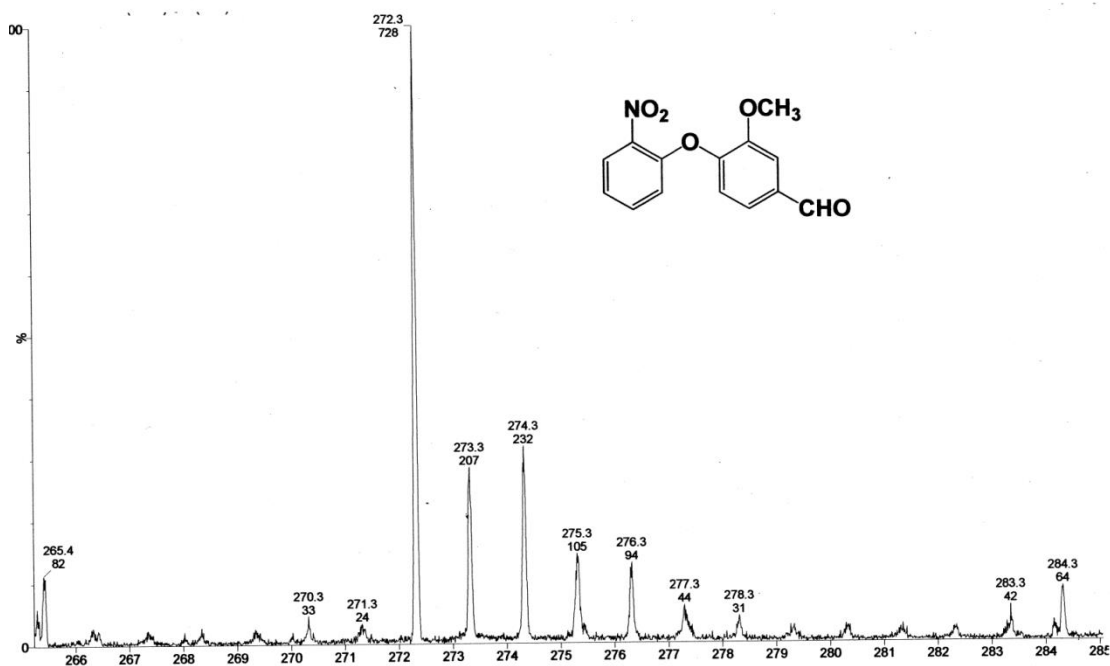


Figure 3.3 Mass spectrum of **DPE-I**

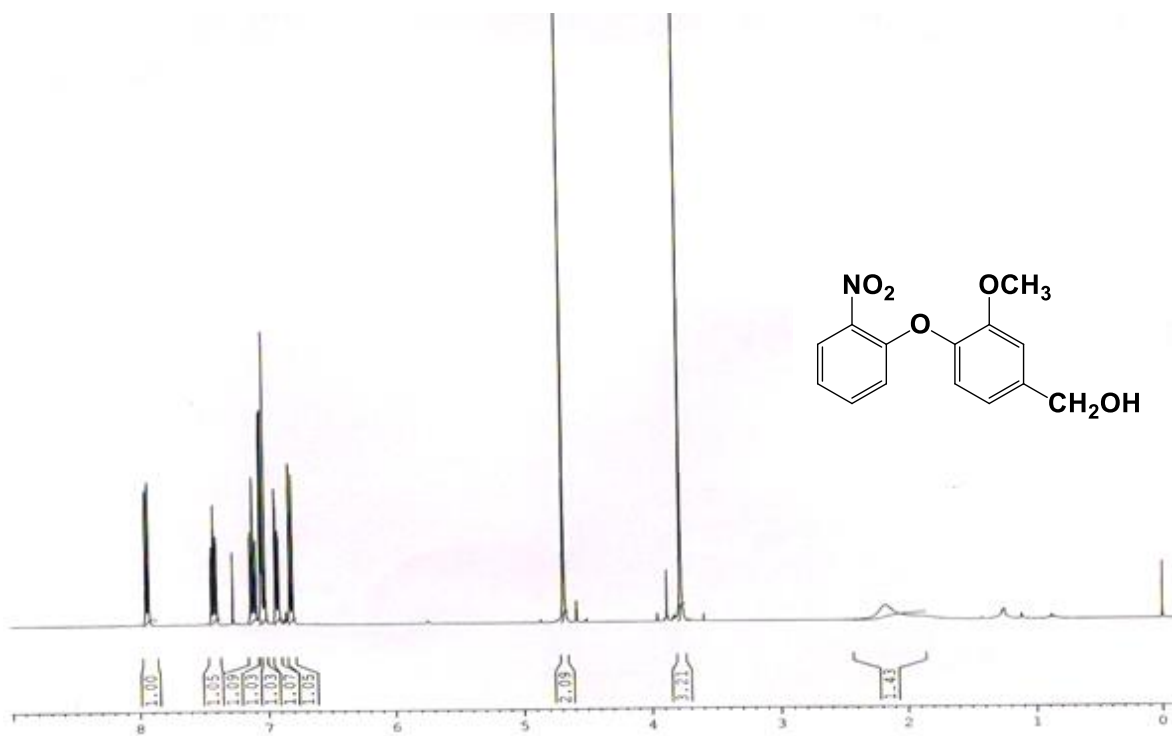


Figure 3.4 ¹H NMR spectrum (400 MHz, CDCl₃) of **DPE-II**

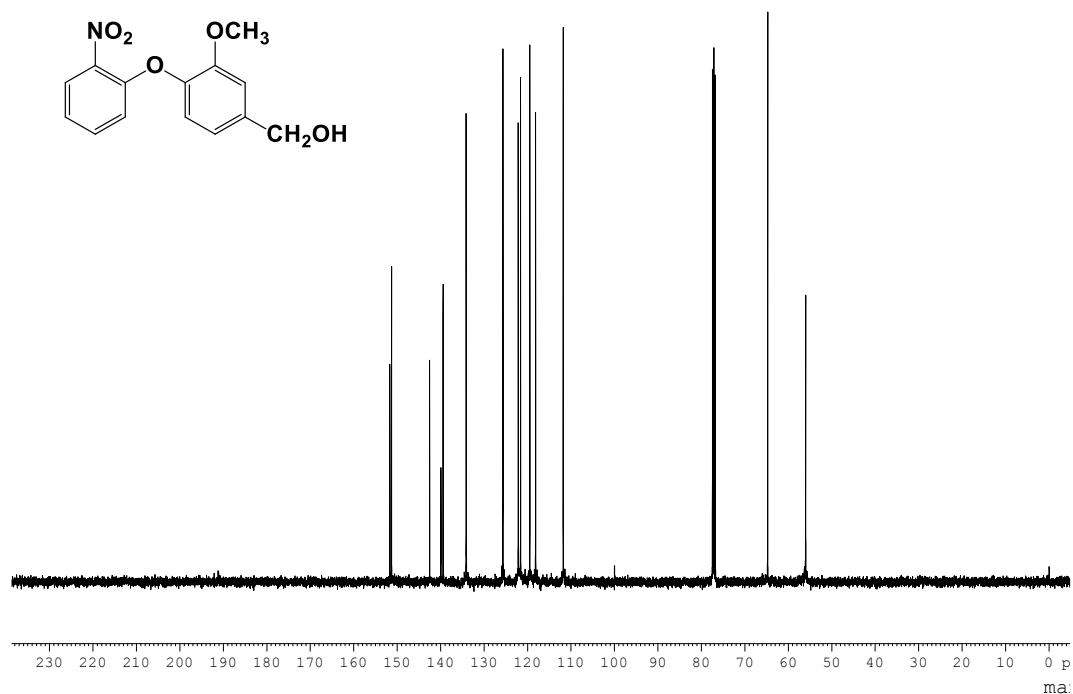


Figure 3.5 ¹³C NMR spectrum (100.6 MHz, CDCl₃) of **DPE-II**

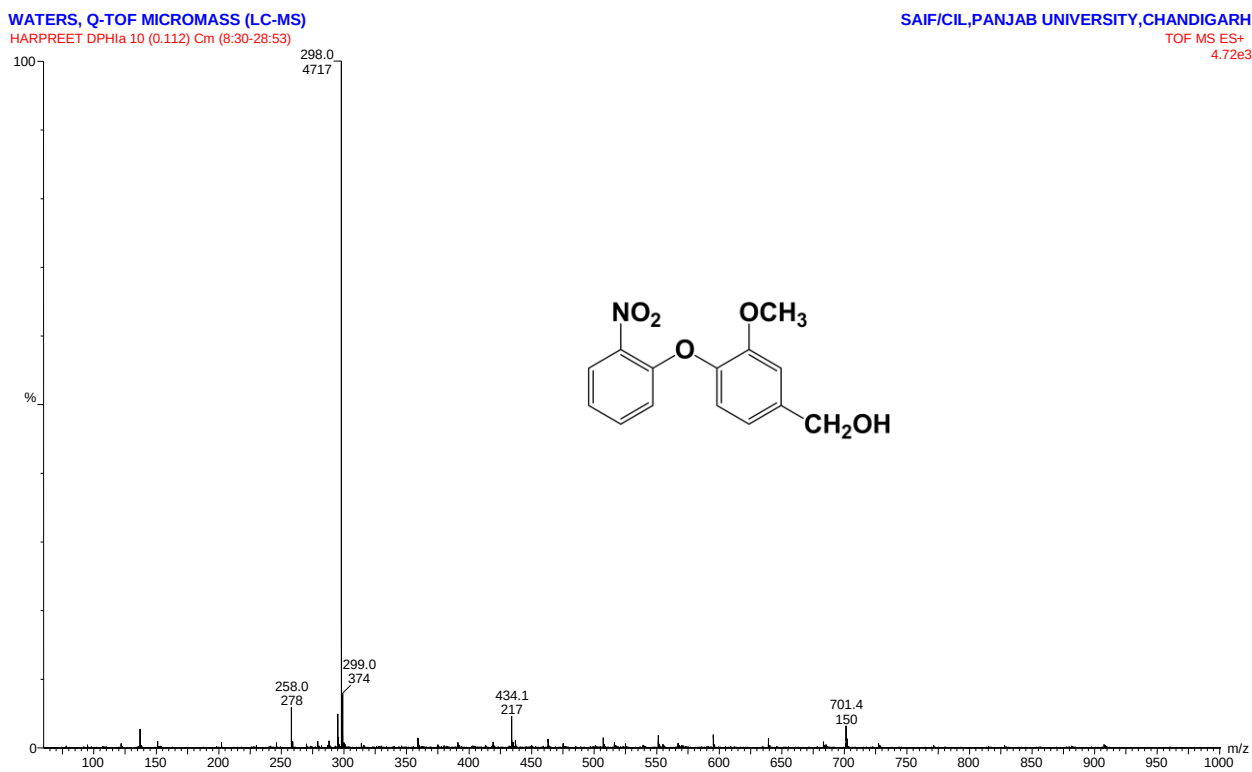


Figure 3.6 Mass spectra of **DPE-II**

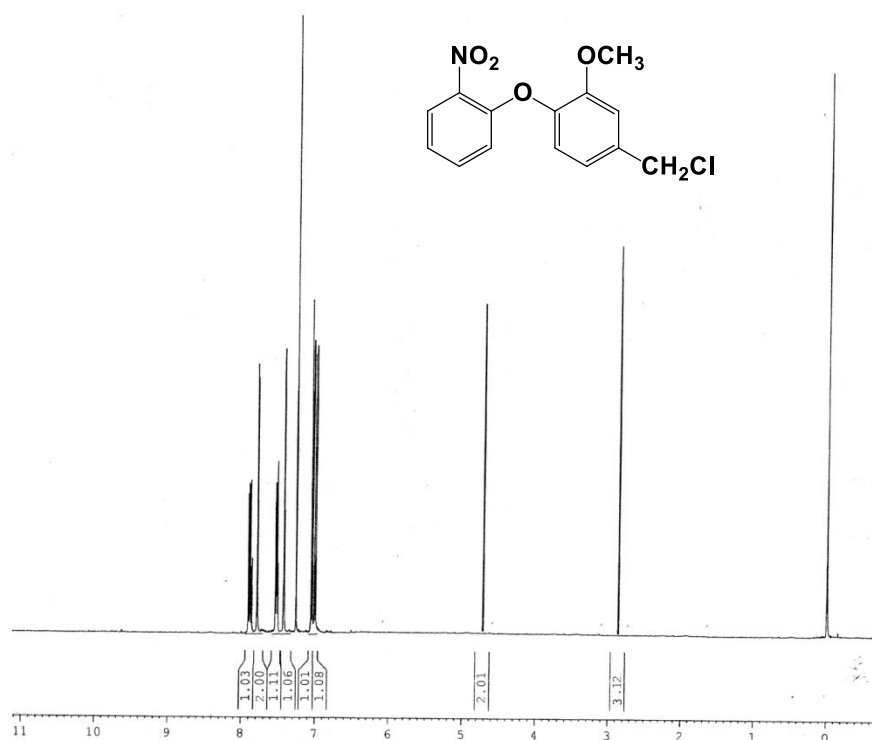


Figure 3.7 ¹H NMR spectrum (400 MHz, CDCl₃) of **DPE-III**

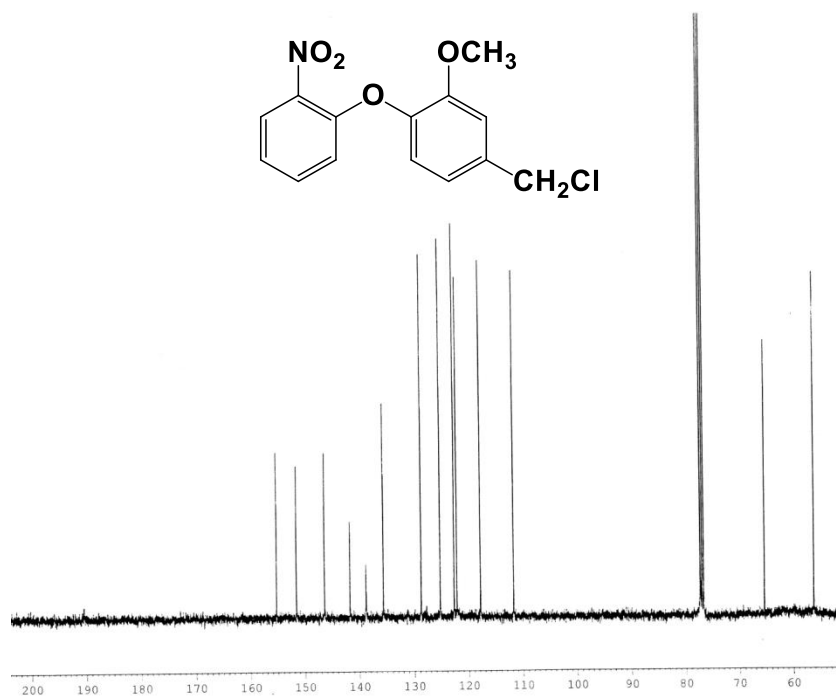


Figure 3.8 ¹³C NMR spectrum (100.6 MHz, CDCl₃) of **DPE-III**

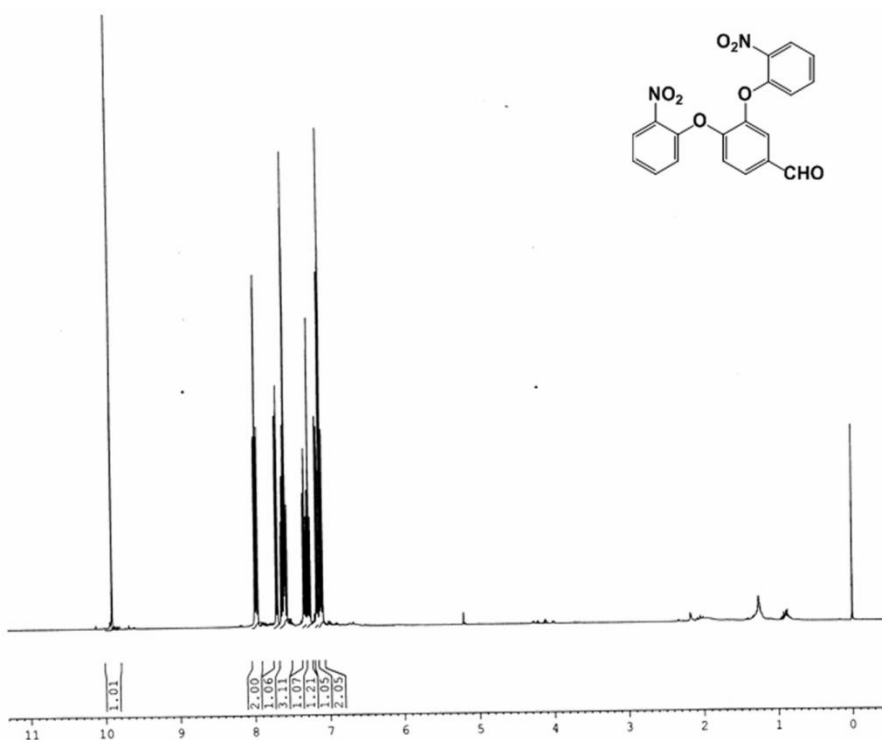


Figure 3.9 ¹H NMR spectrum (400 MHz, CDCl₃) of TPE-I

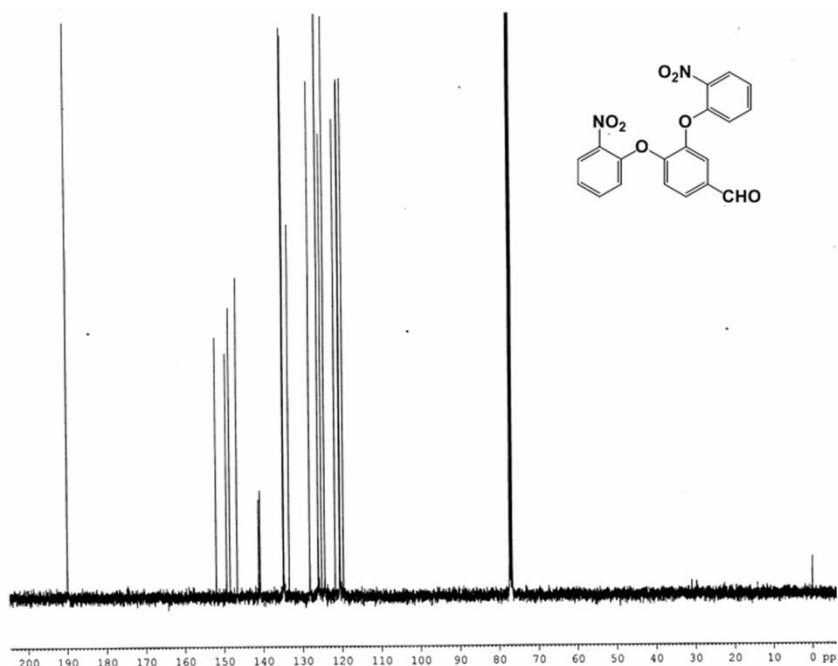


Figure 3.10 ¹³C NMR spectrum (100.6 MHz, CDCl₃) of TPE-I

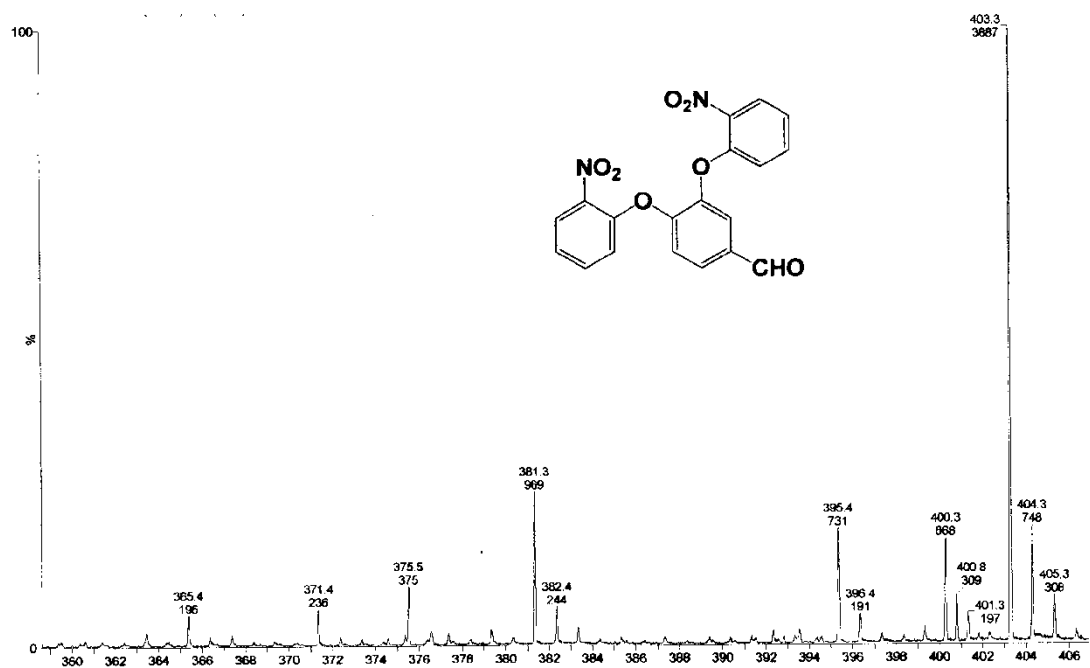


Figure 3.11 Mass spectra of TPE-I

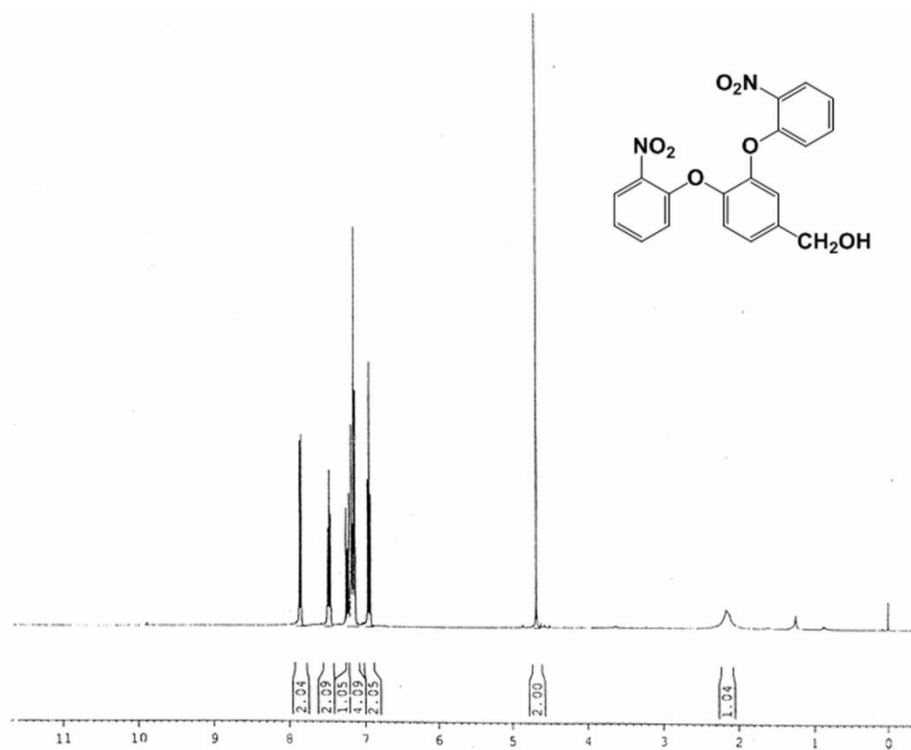


Figure 3.12 ¹H NMR spectrum (400 MHz, CDCl₃) of TPE-II

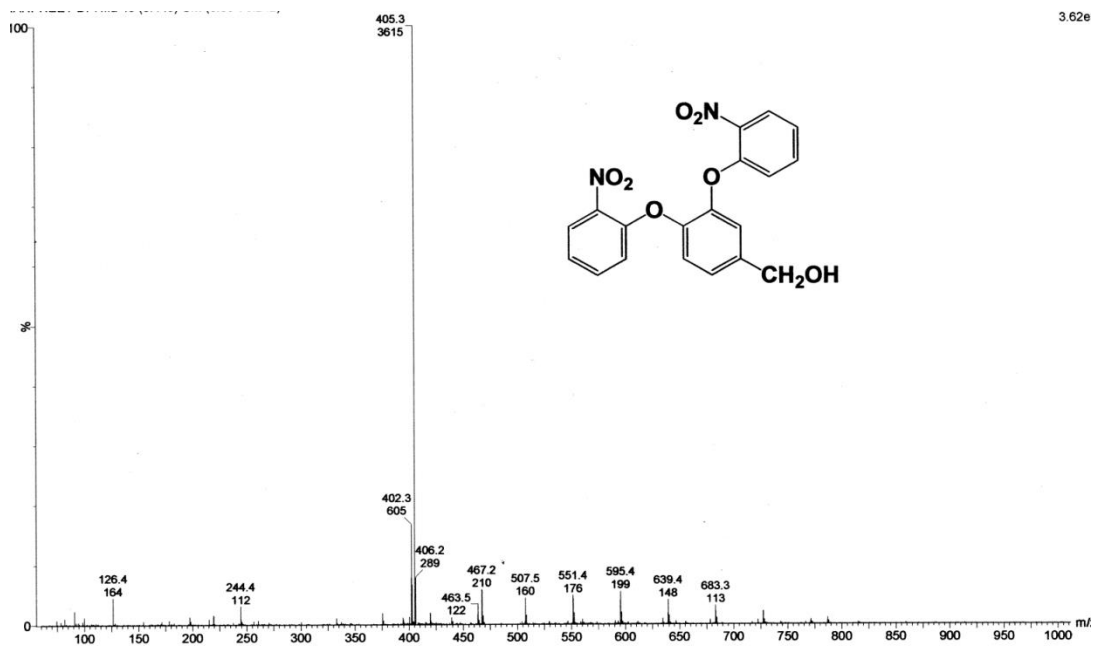


Figure 3.13 Mass spectrum of TPE-II

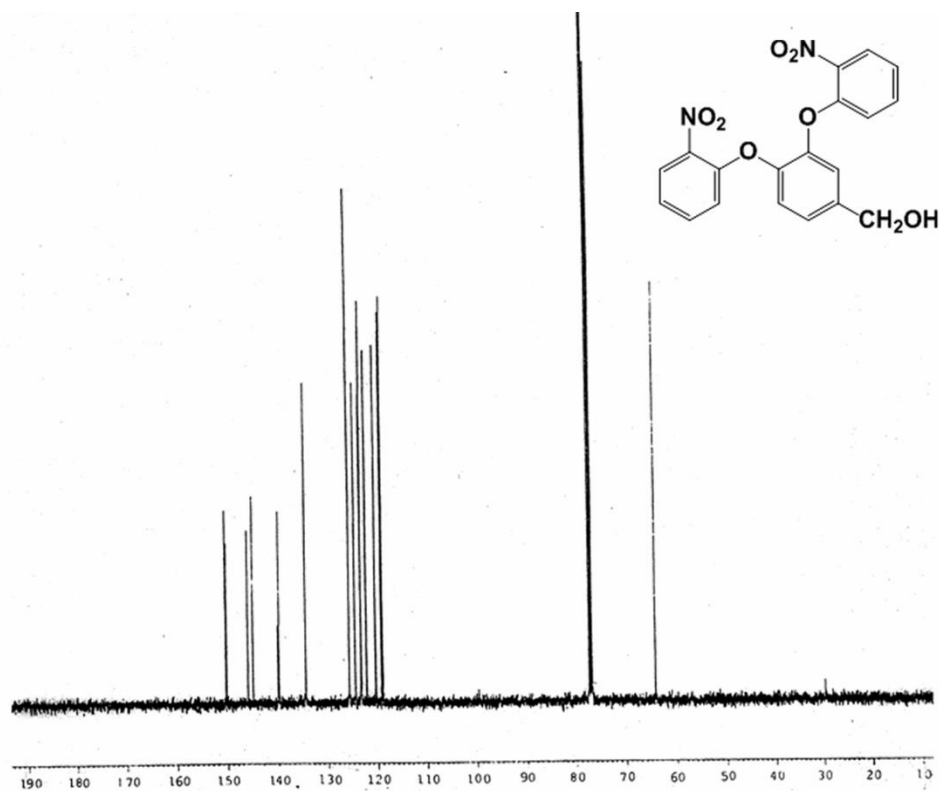


Figure 3.14 ^{13}C NMR spectrum (100.6 MHz, CDCl_3) of TPE-II

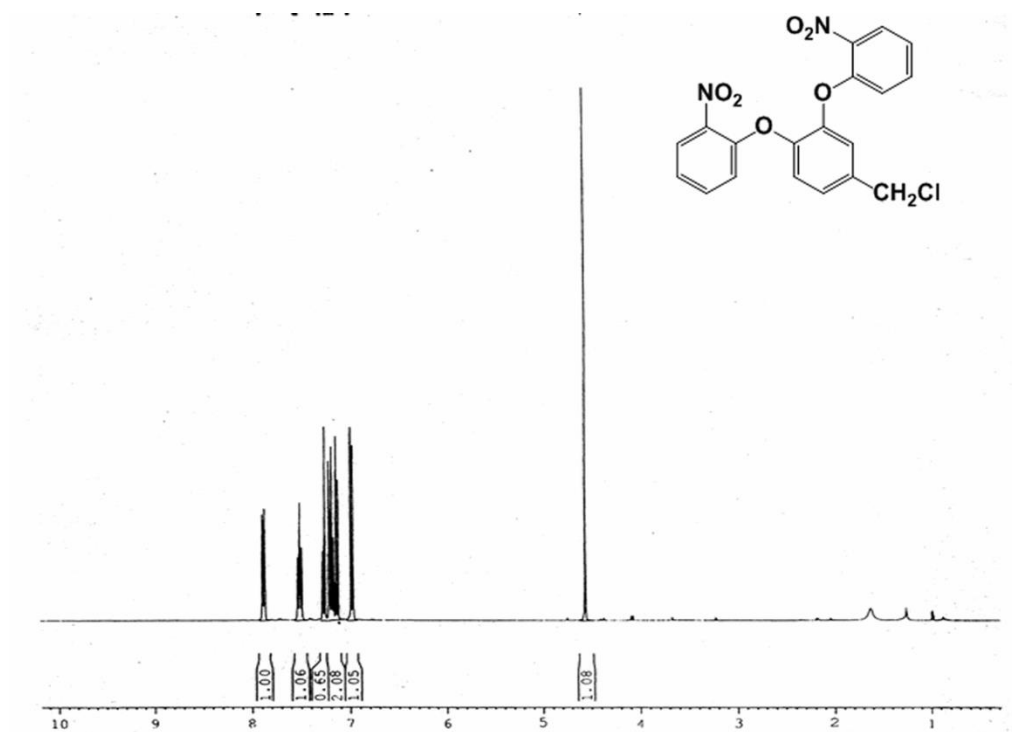


Figure 3.15 ^1H NMR spectrum (400 MHz, CDCl_3) of **TPE-III**

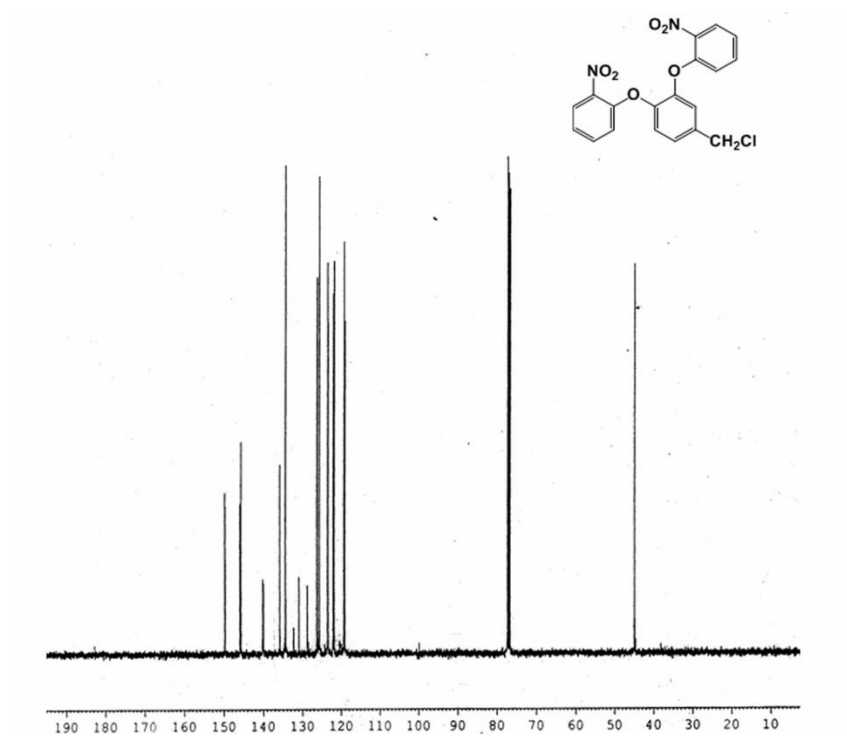


Figure 3.16 ^{13}C NMR spectrum (100.6 MHz, CDCl_3) of **TPE-III**

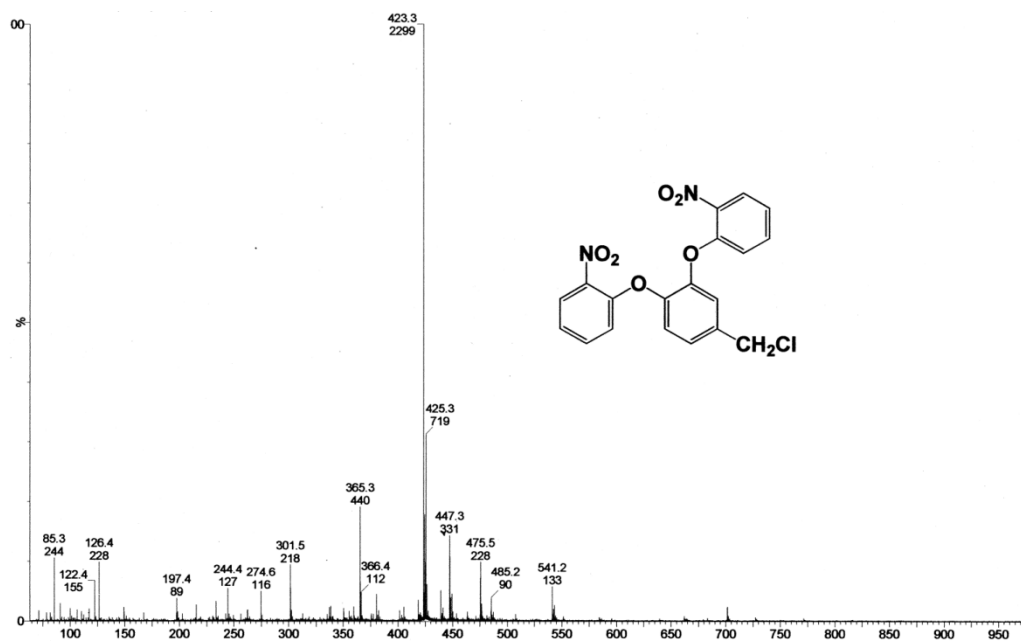


Figure 3.17 Mass spectra of TPE-III

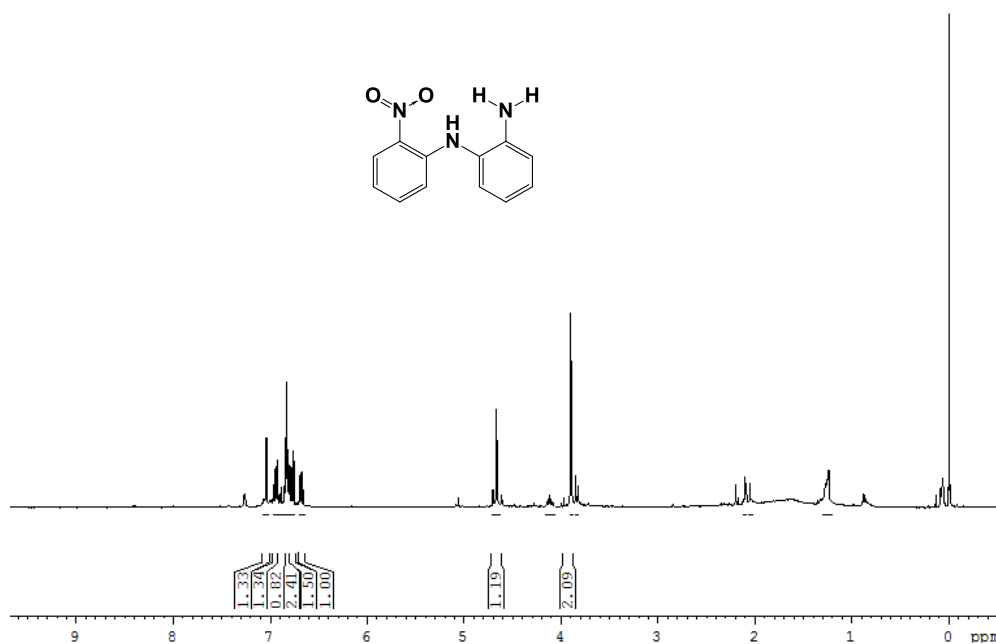


Figure 3.18 ¹H NMR spectrum (400 MHz, CDCl₃) of DPA

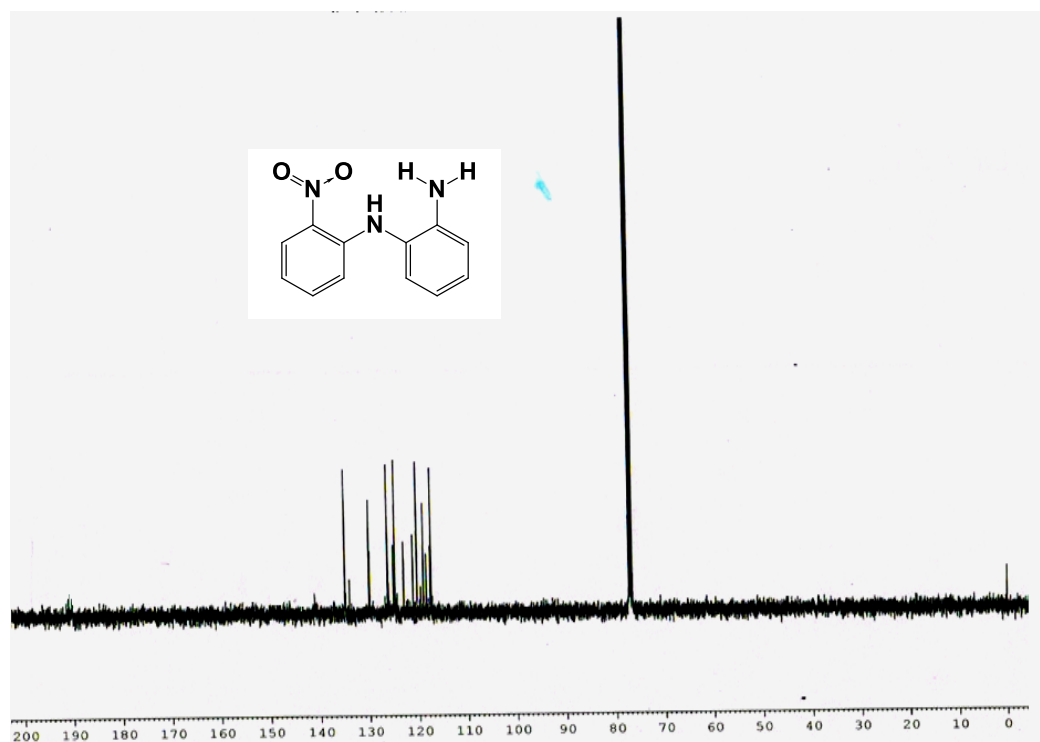


Figure 3.19 ^{13}C NMR spectrum (100.6 MHz, CDCl_3) of **DPA**

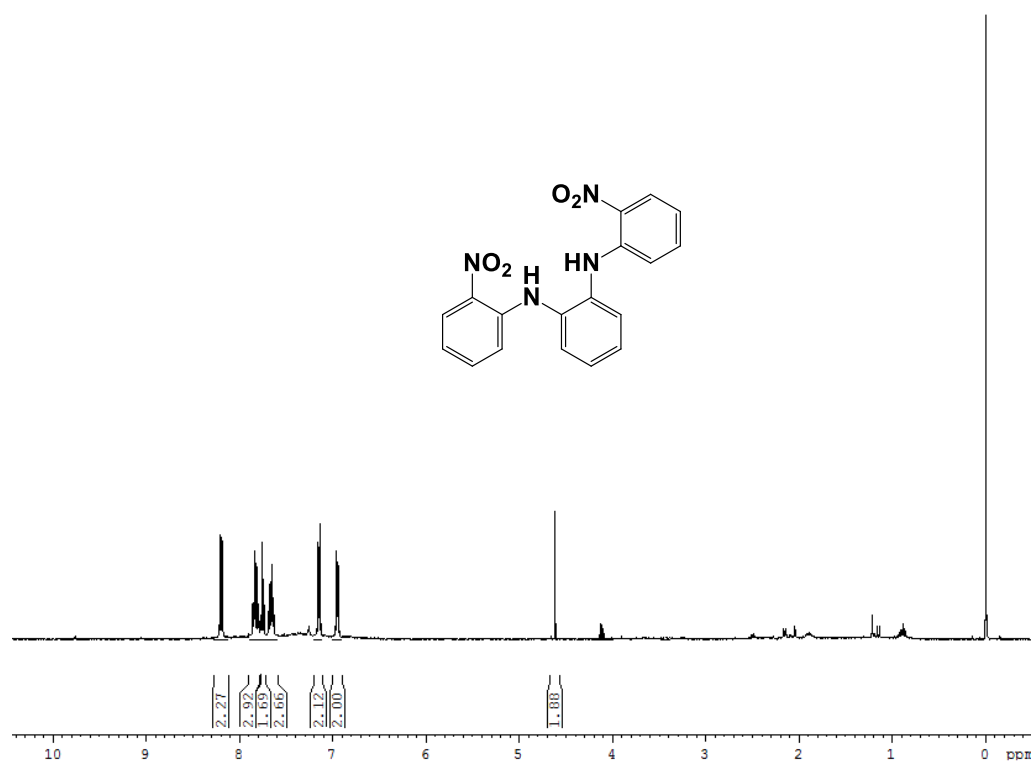


Figure 3.20 ^1H NMR spectrum (400 MHz, CDCl_3) of **TPA**

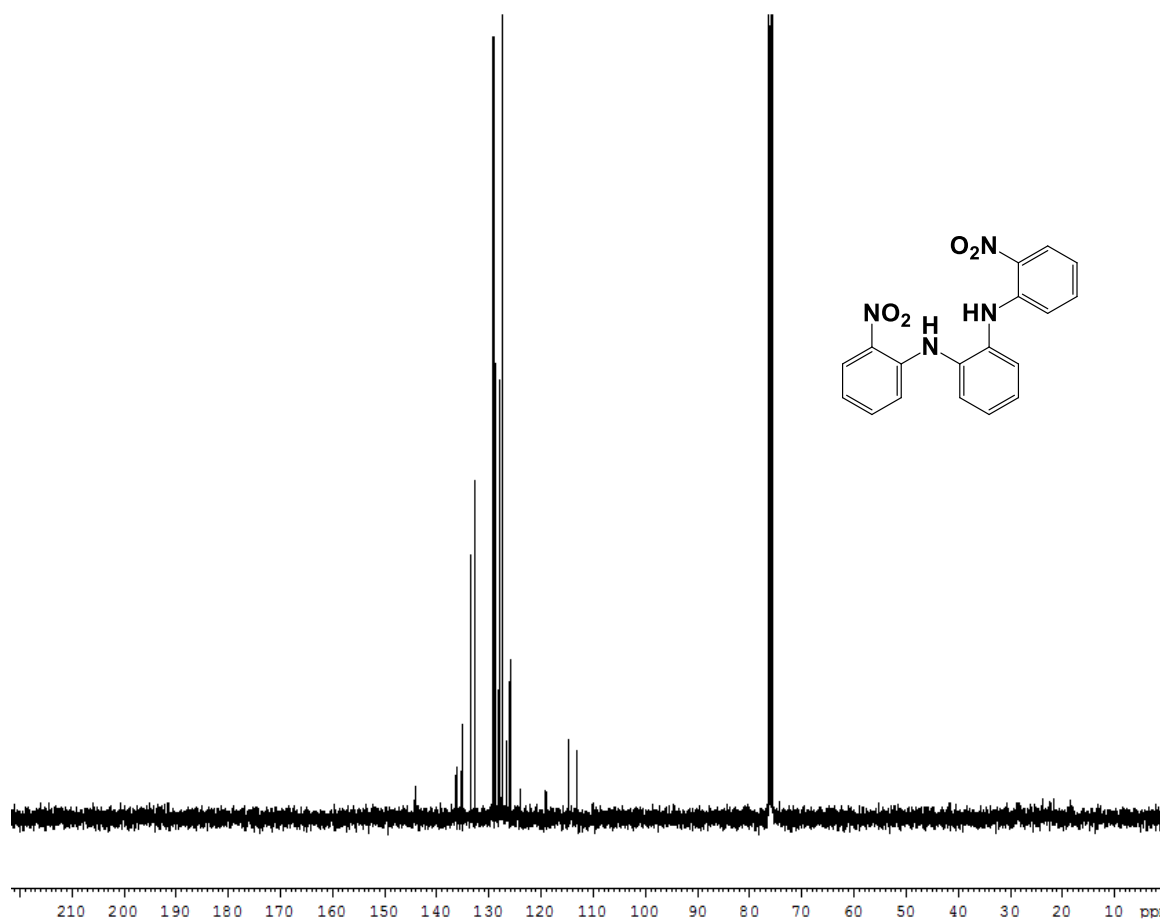


Figure 3.21 ^{13}C NMR spectrum (100.6 MHz, CDCl_3) of TPA

DIPHENYLEETHERS AS ION SELECTIVE ELECTRODES FOR Fe(II) IONS

4a.1 Introduction

Today's fast moving world requires small, fast, economical and easy to operate devices to monitor health, environment, security and many related issues [1]. This requires development of small devices along with a number of molecules that can sense specific chemical or biological species. Various organic ligands with diverse functional groups have been reported in literature [2–7]. Crown ethers were one of the first molecules identified to capture ions [8]. Interestingly, there are very limited number of reports where phenyl ether based molecules have been used for sensing of ions [9]. However, their use as antibacterial agents has been quite popular [10, 11]. The molecules offer the advantage of being rigid, due to phenyl ring and flexible, due to ether linkage. Besides that, placing an appropriate substituent on rest of available positions in the ring offers the benefit of obtaining tunable cavity size.

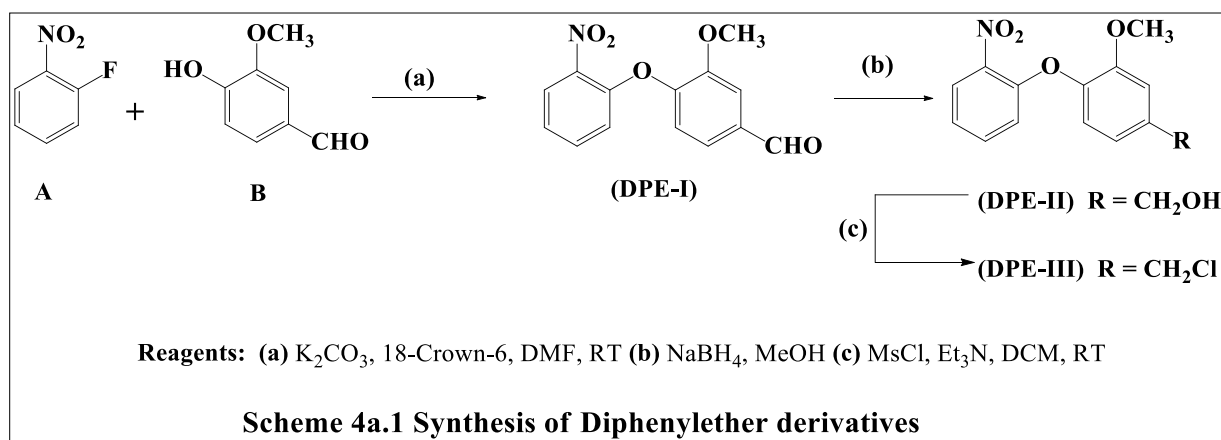
Thus, keeping in view the required delicate balance of “rigidity” (for high selectivity) and “flexibility” (for a sufficiently fast ion exchange) of a sensor molecule, it was interesting to explore the ionophoric potential of diphenylether linkage, which has phenyl units for the required rigidity and as a whole the unit is having reasonable flexibility. For this purpose, three diphenylether derivatives **DPE-I**, **DPE-II** and **DPE-III** were synthesized and their ionophoric potential was tested potentiometrically which is a reliable, selective, and sensitive method for detecting and monitoring cations and anions [12–19]. Potentiometric studies indicate that these ionophores have a strong affinity towards Fe^{2+} ions, which was also supported by theoretical and spectrochemical studies.

Iron is an important element in industrial, medical, biological and environmental studies [20]. It is also present in a variety of rock and soil minerals. It is widely accepted that the presence of iron can have beneficial or adverse effects on the properties of many substances and the nature of various biological systems. Fe(II) is an important constituent of myoglobin, hemoglobin, hemoenzymes, many co-factors involved in enzyme activities and also plays an important role in

oxygen and electron transport [21] as well as in energy metabolism [22]. Thus, maintenance of Fe^{2+} levels is crucially important to human health. However, iron deficiency anemia is one of the world's most common nutritional deficiency diseases [23], at the same time high levels of iron may enhance risk of heart disease, cancer and other illnesses such as haemochromatosis [24]. So, monitoring of iron levels in biological, industrial and environmental samples is very important. There are several methods to determine Fe^{2+} concentration such as colorimetry [25, 26], spectrophotometry [27, 28], potentiometry [29,30], voltammetry [30] and optode measurements [31, 32]. The three diphenylether ionophores **DPE-I**, **II** and **III** were fabricated as potentiometric liquid membrane electrodes selective for Fe(II) ions. Experimental conditions like composition of membrane ingredients, suitable concentration of the internal solution of the electrode, working pH range, working concentration range, detection limit and other response characteristics have been optimized to obtain better potentiometric chemical sensors.

4a.2 Synthesis of Diphenylether derivatives

Ionophores **DPE-I**, **DPE-II** and **DPE-III** were synthesized (**Scheme 4a.1**) using a method reported in the literature [11]. In the first step, ether linkage was formed via nucleophilic aromatic substitution. In this reaction 18-crown-6 was used as a phase transfer catalyst, which



helped in increasing the solubility of nucleophile by offering a softer countercation. Alkali metal cations bound by crown ethers are common lipophilic countercations, which form salts that are soluble in non polar solvents. Thus, in first step the potassium ion of commonly used base K_2CO_3 formed a complex with 18-crown-6 [33, 34], which easily dissolved in DMF by forming salt with the phenoxide ion generated from 3-methoxy-4-hydroxy benzaldehyde (B). Phenoxide ion

then substituted the fluoro group of 1-fluoro-2-nitrobenzene (A) at room temperature yielding **DPE-I**. Then, **DPE-II** was synthesized via reduction of aldehyde group of DPE-I using NaBH₄ and methanol. Spectral data confirms this conversion. The ¹HNMR of DPE-II showed disappearance of signal due to aldehyde group (9.9 ppm) as well as appearance of two new signals at 4.6 ppm (-CH₂OH) and 2.1 ppm (-CH₂OH) corresponding to two methylene protons and one alcoholic proton of hydroxymethyl group. Also, shifting of signal at 190.8 ppm (-CHO) to 64.7 ppm (-CH₂OH) in ¹³CNMR confirms this. Further, mesityl chloride in the presence of an organic base was preferred as the chlorinating agent to convert **DPE-II** into corresponding chloromethyl product **DPE-III** over the traditional methods that often requires strongly acidic reagents as well as harsh reaction conditions [35–39]. Then, the three ionophores were tested for binding with different metal ions by potentiometric studies, theoretical studies and UV-Vis. Spectroscopy.

4a.3 Potentiometric studies On the Liquid Membrane Electrodes

Determination of Formation Constants

The formation constant values indicate the affinity of an ionophore for a particular metal ion. The formation constants of the ionophores with different metal ions were determined by sandwich membrane method [40]. In this method, fused sandwich membrane yield information about activity ratio on both sides of the membrane, where only one side contains the ionophore and other side of the membrane does not contain the ionophore. The membrane potential, E_M, is determined by subtracting the cell potential for a membrane without ionophore from that for the sandwich membrane. Ion-ionophore affinity is easily determined by this method on the basis of transient membrane potential measurement neglecting the ion pairs.

DPE-I, **II** and **III** were interacted with Cu²⁺, Ca²⁺, Mg²⁺, Ni²⁺, Zn²⁺ and Fe²⁺. Formation constant values for different metal ions are shown in Table 4a.1. Highest log K_f values among all cases were observed for Fe²⁺, with **DPE-II** showing highest log K_f value of 8.45 followed by **DPE-I** and **DPE-III** showing values of 8.10 and 7.85, respectively. Table 4a.1 indicates that all the three ionophores form a stable complex with Fe²⁺ as compared to other ions.

Table 4a.1 Formation constants for complexes of ionophores **DPE-I**, **DPE-II** and **DPE-III** with some metal ions using sandwich membrane method

Metal ion	Log K _f		
	DPE-I	DPE-II	DPE-III
Fe²⁺	8.10	8.45	7.85
Zn ²⁺	3.72	3.94	3.21
Ni ²⁺	5.05	4.99	4.82
Ca ²⁺	4.69	5.21	4.36
Mg ²⁺	4.35	4.75	4.31
Cu ²⁺	4.97	5.00	4.43

Optimization of membrane composition

In preliminary experiments, ionophores **DPE-I**, **II** and **III** were used as neutral carriers to prepare PVC based membranes for a variety of metal ions and their responses were observed. Potential response of **DPE-I** towards different metal ions is shown in Figure 4a.1(a). On the basis of these experiments and formation constant values, ionophores were found to show the best response towards Fe²⁺ ions. In all other cases the slope of the corresponding EMF vs $-\log a_M$ calibration curves is much lower than the Nernstian slope for divalent cations. Preferential response towards Fe²⁺ is believed to be associated with selective binding of ionophores with Fe²⁺ ions.

To obtain better electrode properties, like good selectivity, higher sensitivity and a wider working range, the optimization of membrane ingredients is the most necessary part [41, 42]. For this purpose, the amount of ionophore, PVC, o-NPOE and lipophilic ion (NaTPB) were varied to get the optimum composition and its effect on the response characteristics of the electrode, like slope of the calibration curve and detection limit were studied as shown in Table 4a.2. Membrane No. 1 exhibited por detection limit of $1.0 \times 10^{-5} \text{M}$ with a slope of 17.2 mV per decade. The membrane had a composition of 63% of o-NPOE and 1% of **DPE-I**. The sensitivity of the electrode response increased with increasing ionophore content from 1% to 3% with decreased plasticizer content, accordingly.

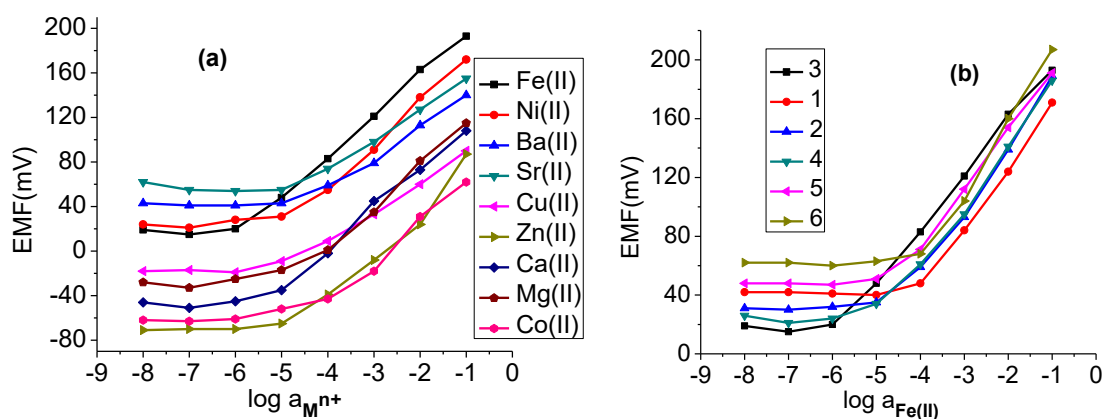


Figure 4a.1 Response of **DPE-I** for (a) different metal ions and (b) different membrane compositions

Table 4a.2 Optimization of membrane ingredients for Fe^{2+} ISE based on Diphenylether derivatives (**DPE-I**, **DPE-II** and **DPE-III**)

Membrane No.	Ionophore	PVC (Wt%)	Plasticizer (Wt%)	Ionophore (Wt%)	NaTPB (Wt%)	Slope, mV/decade	Detection Limit, (M) (Fe^{2+})
1	DPE-I	33	63	1	3	17.2	1.0×10^{-5}
2	DPE-I	34	61	2	3	22.1	3.1×10^{-5}
3	DPE-I	33	61	3	3	27.3	6.3×10^{-7}
4	DPE-I	33	60	4	3	23.3	6.9×10^{-6}
5	DPE-I	32	60	5	3	20.7	2.6×10^{-5}
6	DPE-I	32	59	6	3	19.5	8.3×10^{-5}
7	DPE-II	33	61	3	3	28.1	3.9×10^{-7}
8	DPE-III	32	61	4	3	24.0	6.3×10^{-5}

In case of **DPE-I**, Membrane no.3 having a composition of PVC: o-NPOE: ionophore (**DPE-I**): NaTPB as 33:61:3:3 (wt%) was found to show the best results in terms of slope and detection limit. Further addition of ionophore content from 3% to 6% (Figure 4a.1b), however led to poor response of the electrode which might be due to some in-homogeneity and possible saturation of the membrane. The same composition in case of ionophore **DPE-II** (membrane no.7) showed even better performance. However, **DPE-III** (membrane no.8) was found to show its best possible

response at 4% content. These electrodes i.e., membranes no, 3,7 and 8 were selected for further studies.

Table 4a.3 Effect of internal solution concentration on the potential response of **DPE-I**, **DPE-II** and **DPE-III**.

Ionophore	Internal solution concentration, M	Slope, mV/decade	Detection limit, M (Fe^{2+})
DPE-I	1×10^{-1}	27.3	6.3×10^{-7}
	1×10^{-2}	27.1	7.4×10^{-7}
	1×10^{-3}	23.3	9.5×10^{-7}
DPE-II	1×10^{-1}	28.1	3.9×10^{-7}
	1×10^{-2}	26.9	1.5×10^{-6}
	1×10^{-3}	25.9	1.8×10^{-6}
DPE-III	1×10^{-1}	24.0	6.3×10^{-5}
	1×10^{-2}	24.8	1.0×10^{-5}
	1×10^{-3}	23.9	2.8×10^{-5}

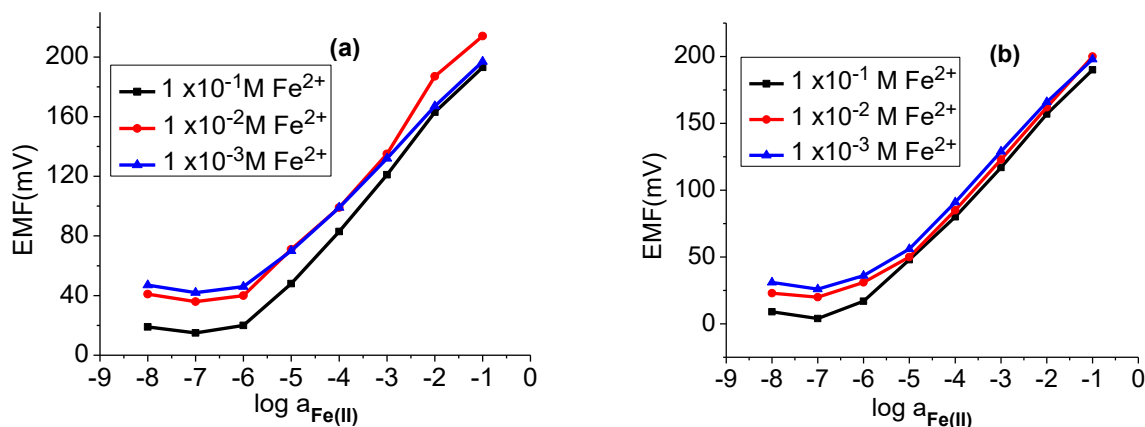


Figure 4a.2 Effect of internal solution concentration on the potential response of (a) **DPE-I** and (b) **DPE-II**

Potentiometric response of ISEs was also affected by the concentration of inner reference solution [43, 44]. Thus, behaviour of the selected membranes at various concentrations of internal solution in the range of $1 \times 10^{-3}\text{M}$ to $1 \times 10^{-1}\text{M}$ was studied. All the ionophores showed slight variation in the slope and detection limit values as shown in Table 4a.3 and Figure 4a.2. It was observed that internal solution concentration of $1 \times 10^{-1}\text{M}$ gave the best response in all cases.

Effect of substituents on calibration characteristics, response time and life time

Calibration curves were drawn for all the electrodes (membrane no. 3,7and 8) for **DPE-I**, **II** and **III**, respectively (Fig. 4a.3) over a concentration range from 10^{-8}M to 10^{-1}M with an internal filling solution of 10^{-1}M of Fe^{2+} ions. As shown in Table 4a.4, all the electrodes showed near Nernstian reproducible slopes. For five repeated measurements, standard deviations of slopes were approximately ± 0.5 mV. The workable concentration range for **DPE-I** and **DPE-II** was found as approximately 10^{-6}M to 10^{-1}M of Fe^{2+} . However, for **DPE-III**, this range reduced to 10^{-5}M to 10^{-1}M of Fe^{2+} . The detection limits, as calculated according to IUPAC recommendation [45], are $6.3 \times 10^{-7}\text{M}$, $3.9 \times 10^{-7}\text{M}$ and $6.3 \times 10^{-5}\text{M}$ for **DPE-I**, **II** and **III**, respectively.

Table 4a.4 Summary of Potentiometric characteristics of best responsive membrane electrodes

Membrane No.& Ionophore	3 DPE-I	7 DPE-II	8 DPE-III
Slope (mV/dec)	27.3	28.1	24.0
LDL (M)	6.3×10^{-7}	3.9×10^{-7}	6.3×10^{-5}
Response Time	20 s	20 s	30 s

Response time is measured by recording emf of the electrode as a function of time. The estimated time to get a stable potential was 20 seconds for **DPE-I** and **DPE-II** (membrane no. 3 and 7) and 30 seconds for **DPE-III** (membrane no. 8). The membrane electrodes could be used for at least 4 months without any measurable drift in working concentration range, detection limit and slopes. After this period, the electrodes behavior gradually decreased. Electrodes were stored in 0.1 M Fe(II) ion solution when not in use to avoid any change in the concentration of ions in the membrane phase.

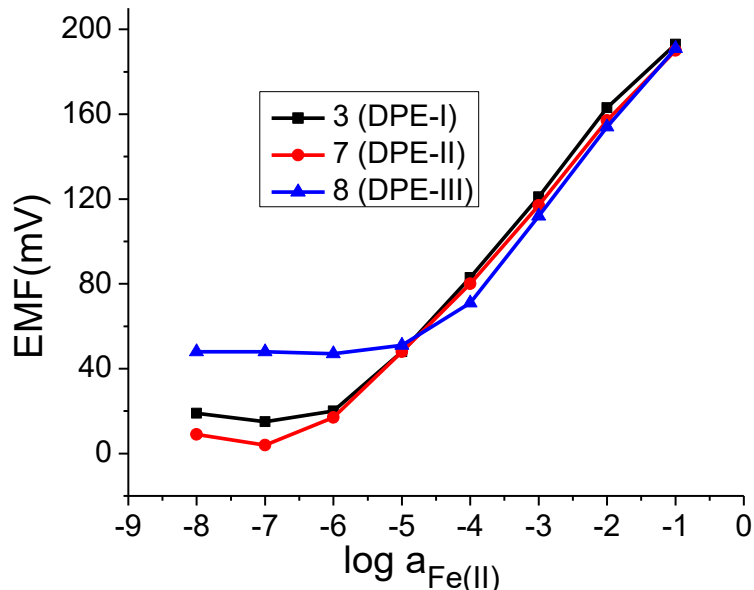


Figure 4a.3 Potentiometric calibration curves for Fe^{2+} selective electrodes based on membrane electrode nos. 3 (**DPE-I**), 7 (**DPE-II**) & 8 (**DPE-III**)

Stability constant values and potentiometric calibration characteristic curves of **DPE-I**, **DPE-II** and **DPE-III** strongly indicate that all the ionophores form stable complexes with Fe^{2+} ion. Lone pairs of ethereal oxygen and oxygen of methoxy group possibly play a major role in this complexation. However, a comparison of potentiometric data of three ionophores clearly indicate that **DPE-II** exhibited best potentiometric characteristics, be in terms of slope, detection limit or stability constant values. The difference observed in the behavior of electrodes could be attributed to the different substituents placed at para position to the ethereal oxygen. The different inductive effects of these substituents $-CHO$, $-CH_2OH$, $-CH_2Cl$ influence the Lewis basicity of ethereal oxygen and hence complex formation. The improvements observed in slope and detection limit values of the hydroxymethyl derivative (**DPE-II**) over its corresponding aldehydic counterpart (**DPE-I**) could be assigned to the replacement of electron withdrawing $-CHO$ group in **DPE-I** by electron donating $-CH_2OH$ group in **DPE-II**. This resulted in an increase of electron density at ethereal oxygen atoms, thus, improving the ionophoric characteristics of the electrode. $-CH_2Cl$ group of the chloromethyl counterpart is even more electron withdrawing in nature and its impact is reflected in the response of membrane electrode no. 8.

Effect of mixed aqueous medium

In order to test the tolerance of electrodes towards partially non-aqueous medium, functioning of the best responsive membrane electrodes (no. 3,7, 8) was investigated in partially non-aqueous media using 10 to 30% (v/v) non – aqueous content in methanol – water, acetonitrile – water and acetone – water mixtures and results are shown in Table 4a.5.

Table 4a.5 Response of Fe^{2+} ISEs **DPE-I**, **DPE-II** and **DPE-III** in mixed solvent media

Solvent	Mixed solvent (%)	Slope, mV/ decade			Detection limit, M (Fe^{2+})		
		DPE-I	DPE-II	DPE-III	DPE-I	DPE-II	DPE-III
Methanol	10	27.2	26.2	24.3	7.9×10^{-7}	6.4×10^{-7}	6.0×10^{-5}
	20	26.3	20.9	22.6	1.5×10^{-6}	3.4×10^{-6}	3.8×10^{-4}
	30	20.6	17.4	19.4	3.1×10^{-6}	8.3×10^{-6}	1.3×10^{-4}
Acetonitrile	10	27.4	27.1	25.4	6.9×10^{-7}	3.9×10^{-7}	3.3×10^{-6}
	20	27.8	27.1	25.8	1.5×10^{-6}	3.8×10^{-7}	6.8×10^{-5}
	30	27.9	26.3	25.0	2.6×10^{-6}	1.5×10^{-6}	4.5×10^{-5}
Acetone	10	26.2	26.6	22.3	2.5×10^{-6}	3.2×10^{-7}	2.2×10^{-4}
	20	25.3	25.1	21.5	2.1×10^{-6}	1×10^{-6}	1.9×10^{-4}
	30	21.5	19.4	20.7	2.1×10^{-6}	3.9×10^{-6}	3.8×10^{-3}

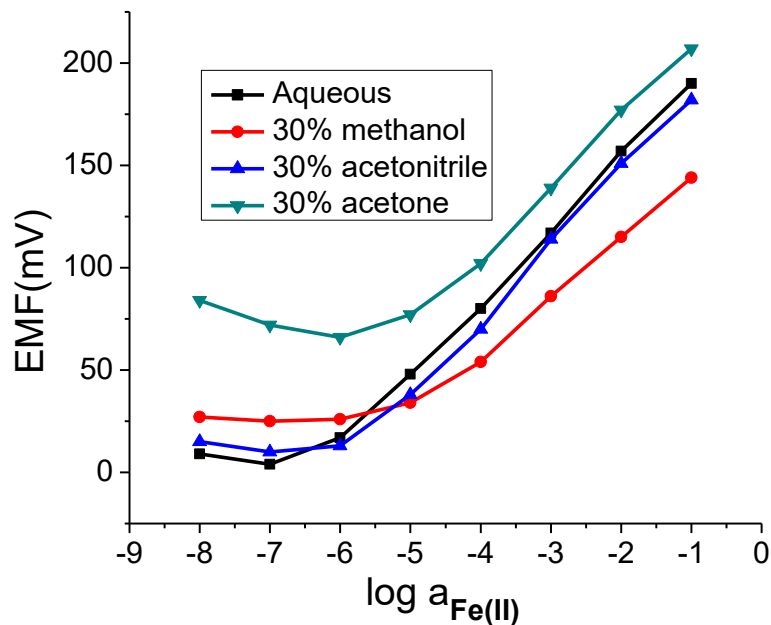


Figure 4a.4 Potential Response of **DPE-II** in different solvents

The membranes do not undergo any appreciable change in detection limit values upto 30% of the non-aqueous content (Figure 4a.4) but slope values were found to decrease beyond 20%, specially in methanol and acetone media. Acetonitrile medium, however, was found to be well tolerated upto 30% in all cases.

Effect of pH

The pH dependence of the potentiometric response of electrodes (no. 3, 7 and 8) was studied in the pH range of 3.0 – 12.0 in the solution of 10^{-3}M concentration of Fe(II) ions. The pH was adjusted by adding small amounts of HCl (0.1 M) or NaOH (0.1 M) as per requirement and results are shown in Figure 4a.5 The emf is independent of pH in the range of 4 – 9 for **DPE-I** and 5 – 8 for **DPE-II** while for **DPE-III**, the pH range with stable potential was approximately 4 – 8. Beyond these limits, however a sharp drift in the potential versus pH was observed. The drift observed at higher pH values could be due to the formation of Fe(OH)_2 in the solution. In acidic solution having low pH values, the ionophores could be protonated to some extent, which resulted in improper functioning of the membrane electrode.

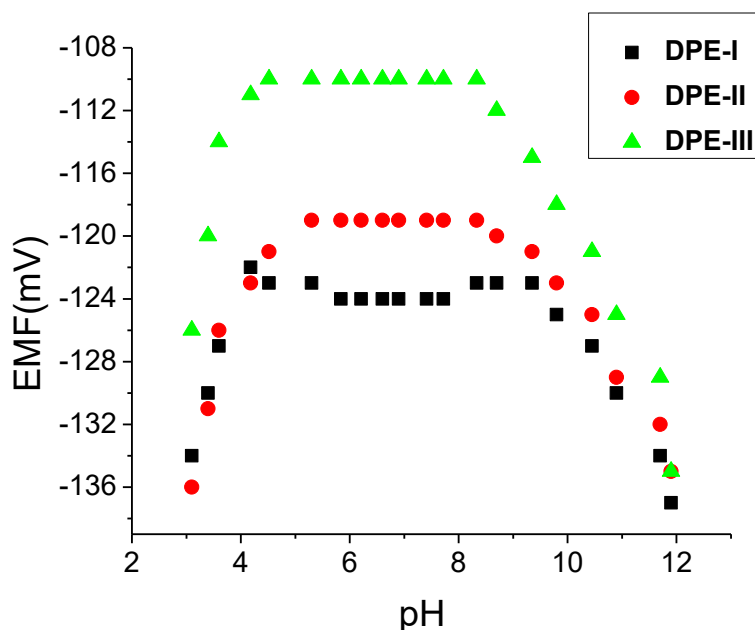


Figure 4a.5 Effect of pH at 1×10^{-3} M Fe^{2+} solution on the potential response of electrodes

Effect of interfering ions on selectivity of the electrodes

Selectivity of an ISE is its ability to respond to one particular ion more than others and is expressed as the potentiometric selectivity coefficient – $\log K_{\text{Fe}^{2+} \text{B}}^{\text{Pot}}$. Potentiometric selectivity coefficient describes preference by the membranes for Fe^{2+} relative to an interfering ion B. Several methods are available for its determination. In this work, potentiometric selectivity coefficients were determined by IUPAC recommended fixed interference method (FIM). In this method, a fixed concentration of interfering ions (1.0×10^{-2} M) and a varying concentration of $\text{Fe}(\text{II})$ ion solution ranging from 1×10^{-8} M to 1×10^{-1} M was used. The potentiometric selectivity coefficients were then determined using the following expression [46]:

$$K_{AB}^{\text{POT}} = \frac{a_A}{a_B^{z_A/z_B}}$$

Where, a_A is the activity of primary ion A at the lower detection limit in the presence of interfering ion B, a_B , the activity of interfering ion B and z_A and z_B are their respective charges.

Table 4a.6 Potentiometric selectivity coefficients of **DPE-I**, **DPE-II** and **DPE-III** by Fixed interference method

Interfering ions	$\log K_{Fe^{2+}, B}$		
	DPE-I	DPE-II	DPE-III
Ni²⁺	-1.3	-1.7	-1.7
Cu²⁺	-1.9	-1.9	-1.9
Sr²⁺	-2.8	-2.9	-2.9
Ba²⁺	-2.9	-2.9	-2.9
Zn²⁺	-2.4	-2.7	-2.7
Co²⁺	-2.3	-2.5	-2.5
K⁺	-1.1	-1.1	-1.1
Ca²⁺	-1.8	-1.8	-1.8
Na⁺	-1.9	-1.9	-1.9
Mg²⁺	-2.1	-2.2	-2.2
Mn²⁺	-2.2	-2.4	-2.4

The values of selectivity coefficients so determined are compiled in Table 4a.6. From the data, it can be concluded that there is no serious interference from common ions. The logK values of **DPE-I**, **II** and **III** are in the range of –2.0 to –2.9 which indicates that proposed electrodes have high selectivity for Fe(II) ions over other ions having similar chemical properties. However, the values observed in case of K⁺ and Na⁺ ions can be associated to the limitations of the FIM as it depends on the charge of the ion.

Potentiometric titration

The analytical applicability of the electrodes was tested by using these as indicator electrodes in the potentiometric titration of Fe²⁺ ion solution. 25 mL of 1×10⁻²M Fe²⁺ solution was titrated

against $1 \times 10^{-1} \text{M}$ solution of EDTA. The titration curve for DPE-II is shown in Figure 4a.6. A very good inflexion point corresponding to 1:1 stoichiometry of the complex was observed, which shows that proposed sensors can be used for the determination of Fe^{2+} ions, potentiometrically.

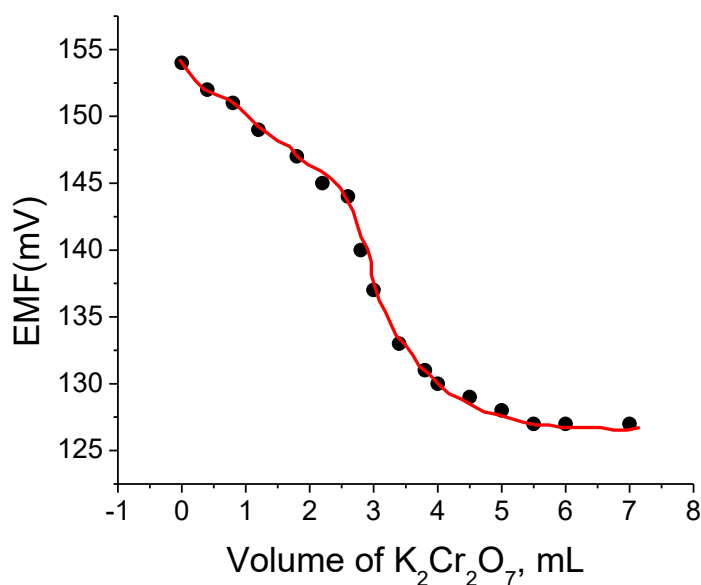


Figure 4a.6 Potentiometric titration of Fe(II) (25 mL of $1 \times 10^{-2} \text{M}$) with $\text{K}_2\text{Cr}_2\text{O}_7$ ($1 \times 10^{-1} \text{M}$) using Fe(II) selective electrode based on **DPE-II**

4a.4 Quantum chemical studies

In an attempt to better understand nature of the ionophores and their interaction with metal ions, theoretical studies were carried out using density functional theory method. B3LYP function with 6-31G and LANL2DZ basis sets were used for quantum chemical calculations of ionophores independently and along with Fe^{2+} ions on Gaussian 03W programme. As shown in Figure 4a.7, ionophores **DPE-I**, **II** and **III** have three dimensional structures. Optimized geometries of all ionophores reflect the presence of a pseudo cavity constituted by the oxygen of methoxy group, nitrogen of nitro group and ethereal oxygen. In the presence of Fe^{2+} , the nitro group lying ortho to the ether oxygen aligns itself in a way so as to generate the best fit metal ionophore complex. The values of energy optimization of uncomplexed and complexed ionophores confirm an overall increase in the stability of all systems after complexation. Energy of **DPE-I** decreases from -970 a.u. to -2233 a.u. , of **DPE-II** decreases from -972 a.u. to -2235

a.u. and of **DPE-III** lowers from – 912 a.u. to – 1033 a.u after addition of Fe^{2+} , thus indicating the formation of highly stable Ionophore – Fe^{2+} complexes. Further, the HOMO – LUMO gap of ionophores and their ferrous ion complexes were calculated at B3LYP/ 6-31G/LANL2DZ levels. It was observed that the gap between HOMO – LUMO is less for DPE-I- Fe^{2+} , DPE-II- Fe^{2+} and DPE-III- Fe^{2+} complexes as compared to ionophores **DPE-I**, **DPE-II** and **DPE-III** alone as shown in Table 4a.7. The frontier molecular orbitals i.e., HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) play an important role in chemical stability and UV-Visible spectra [47 – 48]. As shown in Figure 4a.8, the HOMO for ionophores are distributed over both the phenyl rings, whereas the LUMO is distributed mainly over the phenyl ring carrying nitro group. In case of ionophore – ferrous ion complexes however LUMO seems to be the main contributor in electronic transitions. The decrease of HOMO-LUMO energy gap after complex formation is in agreement with the bathochromic shift observed in absorption spectra.

Table 4a.7 Energy values (a.u.) of HOMO and LUMO of **DPE-I**, **DPE-II**, **DPE-III** and their ferrous ion complexes

Ionophore / Ionophore – Fe^{2+}	Energy in a.u.		
	E_{HOMO}	E_{LUMO}	E_{Gap}
DPE-I	-0.2450	-0.0963	0.1487
DPE-I + Fe^{2+}	-0.4715	-0.4301	0.0414
DPE-II	-0.2335	-0.0926	0.1409
DPE-II + Fe^{2+}	-0.4824	-0.4232	0.0592
DPE-III	-0.2451	-0.1028	0.1423
DPE-III + Fe^{2+}	-0.4831	-0.4329	0.0502

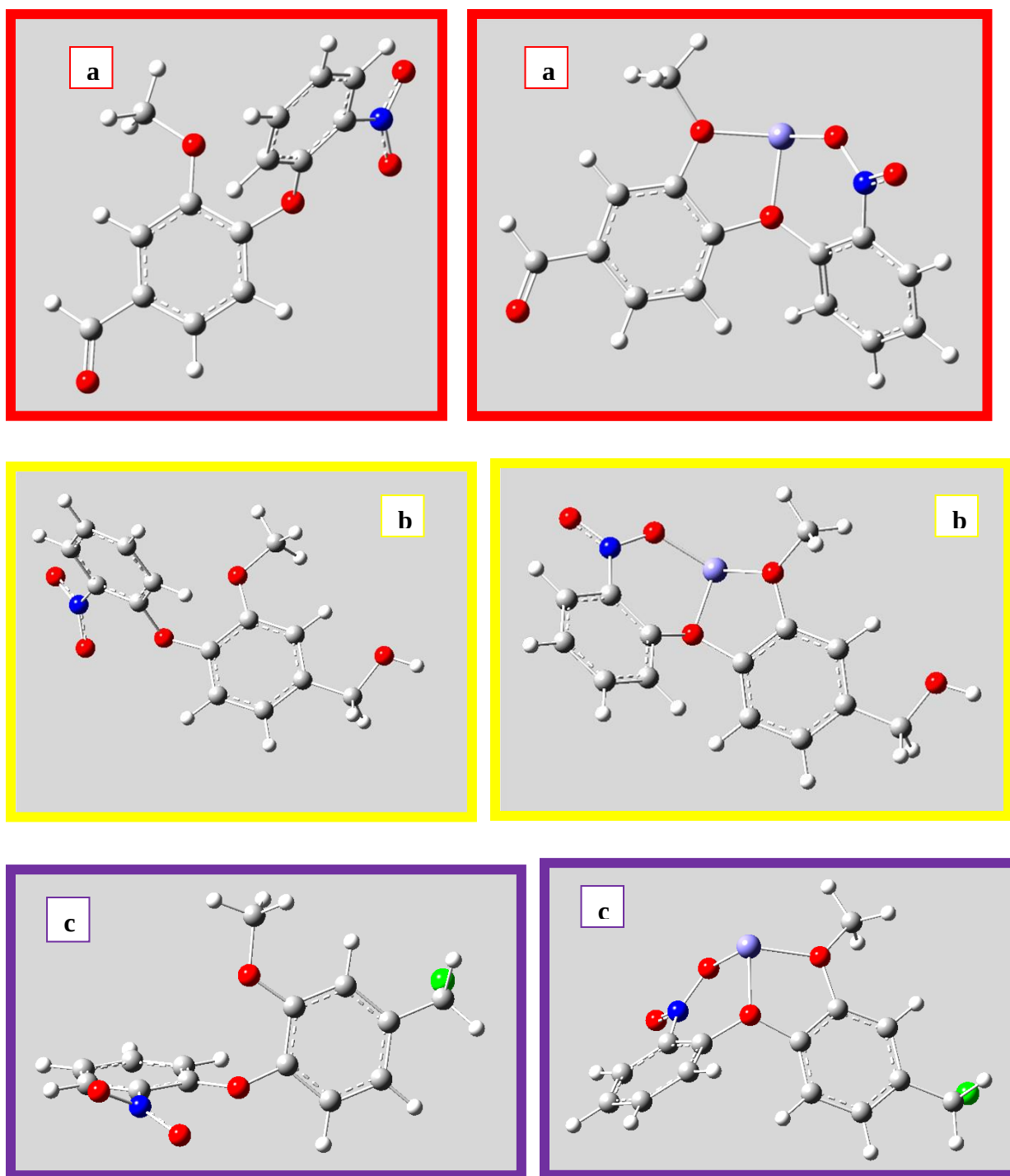


Figure 4a.7 DFT optimized structures of (a) **DPE-I** (b) **DPE-II** (c) **DPE-III** and their Fe^{2+} complexes. White, Red, Blue, Grey, parrot green and purple spheres refer to H, O, N, C, Cl and Fe^{2+} , respectively

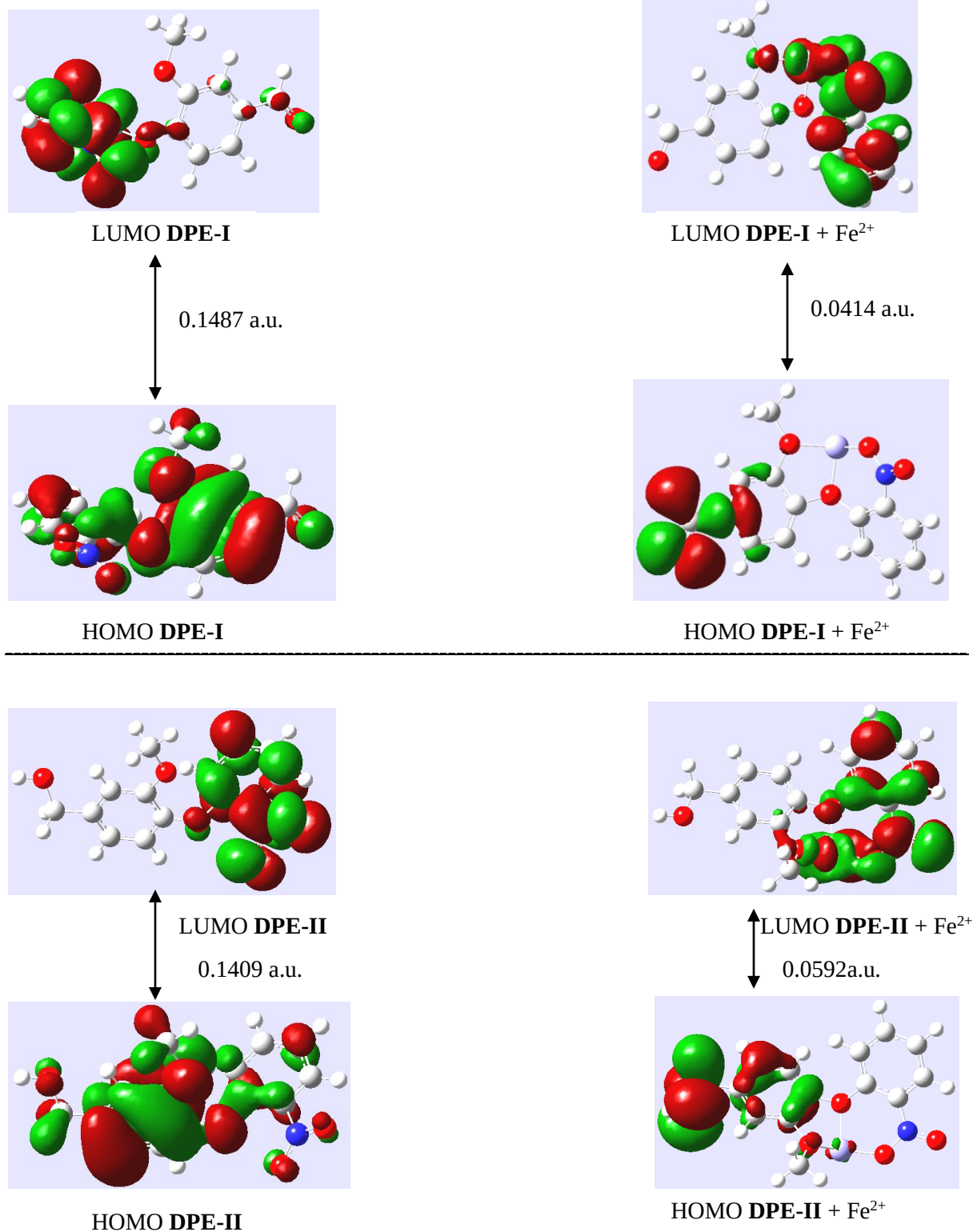


Figure 4a.8 The homo – lumo gap of **DPE-I**, **DPE-II** and their Fe^{2+} complexes calculated at the B3LYP / 631G level

4a.5 Molecular Absorption Spectroscopic studies

Affinity of diphenylethers towards Fe^{2+} ions was further confirmed through U.V.-Visible absorption studies. For this purpose, UV-Vis spectroscopic studies of compound **DPE-I** (40 μM) were performed in acetonitrile – water medium (10 mM HEPES in CH_3CN : H_2O 8:2, v/v) at $\text{pH } 7.0 \pm 0.1$. **DPE-I** showed two intense absorption bands at 262 nm and 309 nm due to $n \rightarrow \pi^*$ excitations involving aldehyde and nitro groups respectively [49].

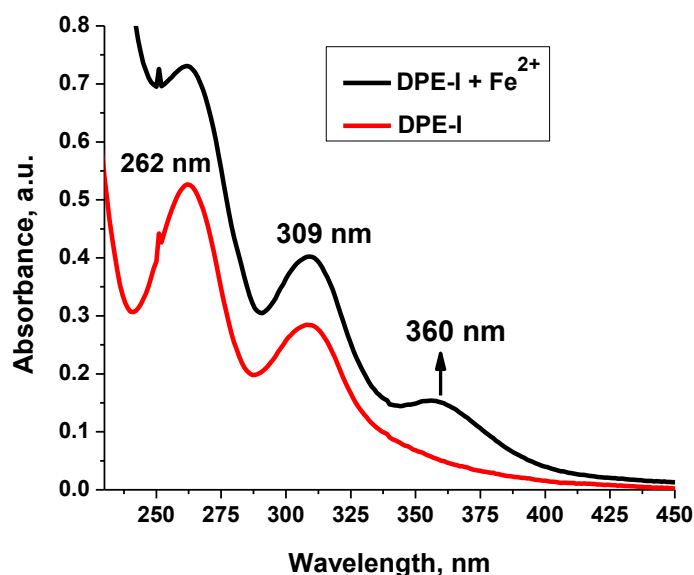


Figure 4a.9 UV – Vis. absorption spectra of pure **DPE-I** (40 μM) and in the presence of one equivalent of Fe^{2+} ions in CH_3CN : H_2O (8:2 ; v/v) at $\text{pH } 7.0 \pm 0.1$ (10 mM HEPES)

No noticeable change in the absorption spectra of **DPE-I** was observed upon addition of different metal ions like Na^+ , Co^{2+} , K^+ , Cu^{2+} , Ni^{2+} , Zn^{2+} and Mg^{2+} (40 μM) to a solution of **DPE-I** in acetonitrile – water medium. However, addition of 40 μM of Fe^{2+} generates a new band at 360 nm with simultaneous increase in the intensity of peak at 309 nm as well as flattening of peak at 262 nm, as shown in Figure 4a.9. Appearance of new band and other changes in spectra indicates the formation of a complex between **DPE-I** and Fe^{2+} ions. Competitive experiments were carried out with other metal ions in the presence of Fe^{2+} ions and no significant interference was observed as shown in Figure 4a.10.

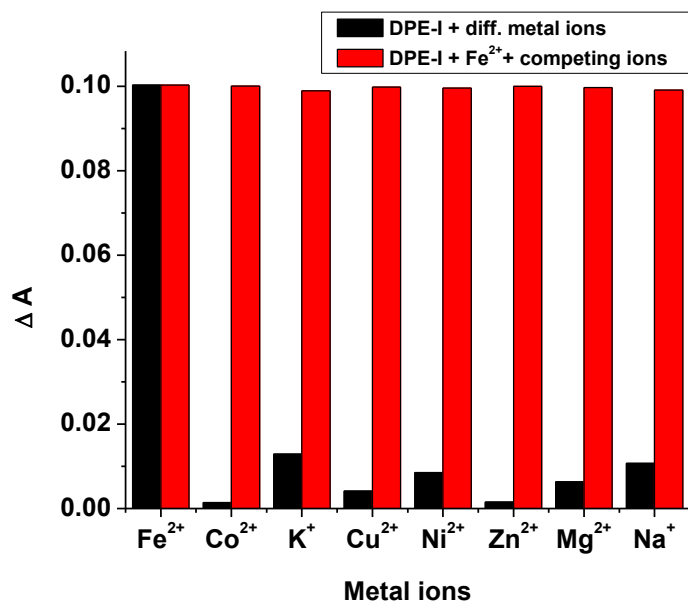


Figure 4a.10 Selectivity of **DPE-I** (40 μM) for Fe^{2+} ions in the presence of other competitive metal ions. Black bars indicate change in absorbance at 360 nm after the addition of 40 μM of the particular metal ion in a 40 μM solution of **DPE-I**. Red bars represent the subsequent addition of same equivalents of Fe^{2+} ions in each of the samples

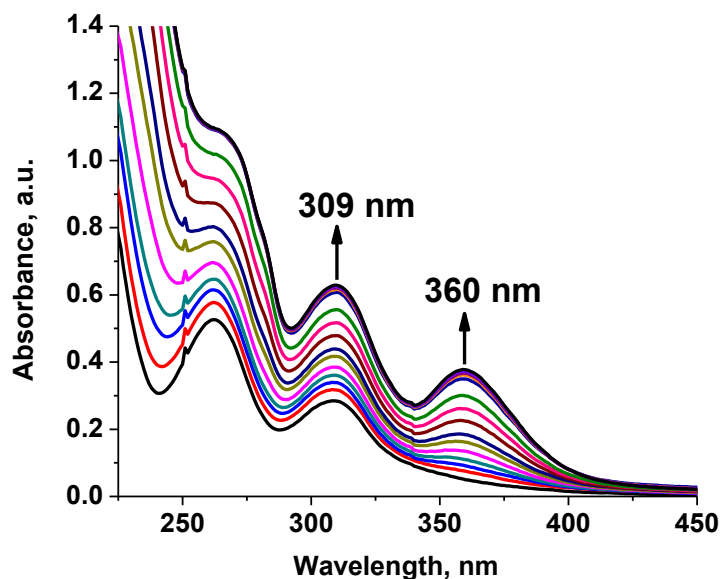


Figure 4a.11 UV–Vis. absorption spectra of **DPE-I** (40 μM) in the presence of different concentrations of Fe^{2+} ions (0.04 – 4.0 equivalents)

Sensitivity of **DPE-I** for ferrous ions was examined with the titration of different concentrations of ferrous ions (0.04 – 4.0 equiv.) in mixed solvent medium (10 mM HEPES in CH₃CN: H₂O 8:2, v/v) (Figure 4a.11). Gradual addition of Fe²⁺ to the solution of **DPE-I** flattens the peak at 262 nm, whereas peaks at 309 nm and 360 nm continuously grow in intensity and reached saturation at about 3.8 equivalents of ferrous ions. Results from these experiments indicated that the absorbance change (ΔA) at 360 nm varies linearly ($R^2 = 0.9927$) to the concentration of Fe²⁺ ions with a lower detection limit of 4.75 μM as shown in Figure 4a.12.

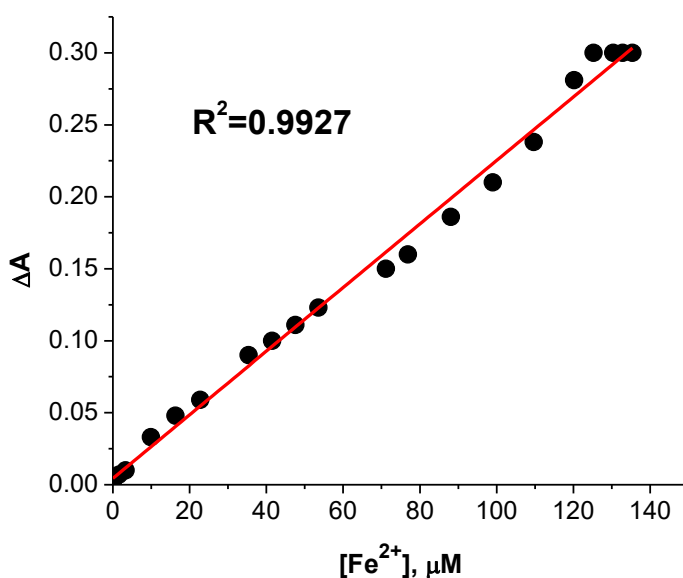


Figure 4a.12 Absorbance changes of **DPE-I**(40 μM) at different concentrations of Fe²⁺ in acetonitrile-water medium. After 3.8 equiv. absorbance becomes almost constant. Detection limit calculated was $4.75 \times 10^{-6} \text{ mol L}^{-1}$

Further Benesi- Hildebrand method was used to check the binding stoichiometry as well as the stability constant (K_a) of **DPE I** – Fe²⁺ complex using the following Benesi-Hildebrand equation [50]

$$\frac{1}{\Delta A} = \frac{1}{\Delta A_{\text{Sat.}}} + \frac{1}{\Delta A_{\text{Sat.}} K_a [\text{Fe}^{2+}]}$$

Where, ΔA is the absorbance difference between the **DPE I** – Fe²⁺ complex and free **DPE-I** at 360 nm and ΔA_{sat} is the maximum absorbance difference at this wavelength. These values were obtained from the UV – Visible titration data. The stability constant was evaluated graphically by

plotting $1/\Delta A$ against $1/[\text{Fe}^{2+}]$ which gave a straight line. K_a value was obtained from the slope and intercept of this straight line.

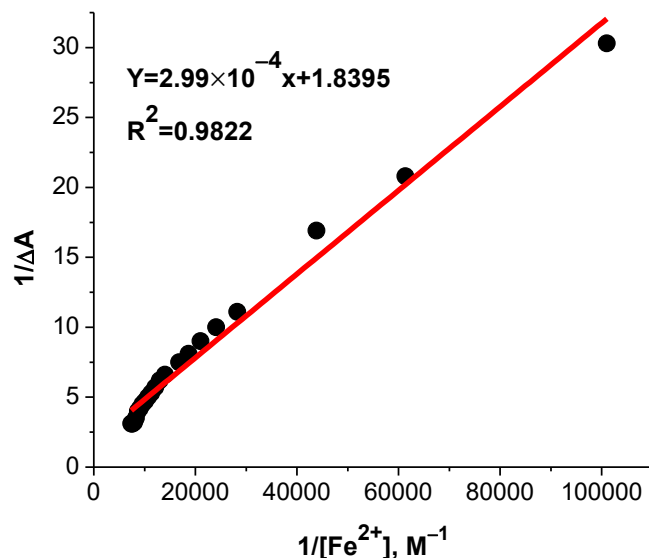


Figure 4a.13 Benesi – Hildebrand plot of **DPE-I** with Fe^{2+} . The monitored wavelength was 360 nm and the binding constant was $6.1 \times 10^3 \text{ M}^{-1}$

As shown in Figure 4a.13, the measured absorbance value $1/\Delta A$ at 360 nm varied as a function of $1/[\text{Fe}^{2+}]$ in a good linear relationship ($R^2=0.9822$), which was an indication of the 1:1 association of the ionophore and Fe^{2+} ions. The association constant calculated from the slope of the straight line was $6.1 \times 10^3 \text{ M}^{-1}$.

Table 4a.8 Comparison of the proposed electrodes with the reported Fe^{2+} selective electrodes

S. no	Ionophore	Detection limit, $\text{mol} \cdot \text{L}^{-1}$	pH Range	Slope (mV/decade)	Ref
1	2,4,6-tri(2-pyridyl)-1,3,5-triazine	5.0×10^{-7}	2.5 - 7.0	30.5 ± 0.1	21
2	N-phenylaza-15-crown-5 (NPA15C5)	7.5×10^{-7}	5.0 - 7.0	29.2	29
3	Polypyrrole	8.78×10^{-7}	-----	29.7 ± 0.5	51
4	2,6-bis-(carboxamide methyl ester) pyridine derivative	4.0×10^{-6}	5.0 - 9.0	31.5 ± 0.5	52
5	Tetra phenyl porphyrin (TPP)	9.6×10^{-7}	3.0 - 5.0	29.4 ± 0.6	53
6	* Proposed ionophore (DPE-II)	3.9×10^{-7}	4 - 10	28.1	Present study

4a.6 References

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TRIPHENYLEETHERS AS ION SELECTIVE ELECTRODES FOR Ca(II) IONS

4b.1 Introduction

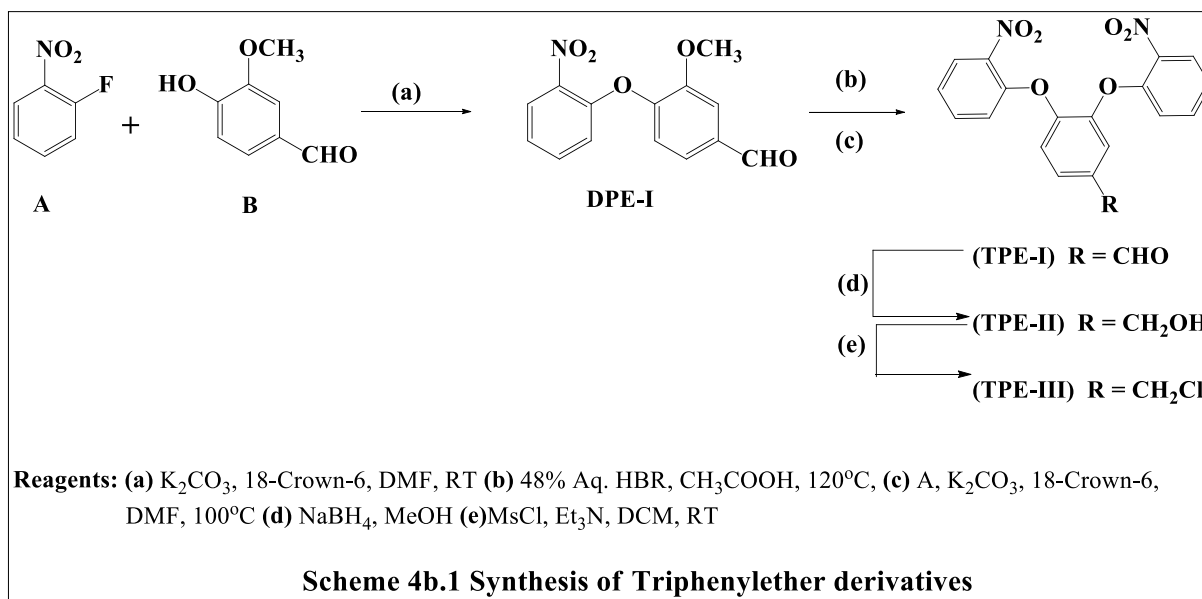
Calcium is fifth most abundant element on earth and the most prevalent cation found in the body. Many physiological processes are controlled, regulated or triggered by calcium ion [1, 2]. It plays a critical role in the activation of enzymes, complexation with nucleic acids, nerve impulse transmission, regulating heart's rhythm and carbohydrate metabolism [3, 4]. Monitoring the presence and concentration of calcium in water is an important parameter in industry [5]. Clinically, monitoring of Ca^{2+} is significant in organ-transplantations and exchange transfusion due to rapid change in its concentration [6-8]. Thus, design and development of specific calcium ion sensors with high selectivity and sensitivity is of great importance. There are a number of reports where selective and sensitive ligands have been developed for the detection of Ca^{2+} in the biological media [9-12].

Also, there is a dire need to develop simple, accurate and low cost methods for the determination of biologically relevant ions to make health care facilities affordable to common man. Several methods have been in use for the quantitative determination of calcium. This includes absorption or emission spectroscopy [13-17], use of ion selective electrodes [18-22], voltammetry [23] and ion exchange methods [24-26]. Amongst all, spectroscopic technique remains the methods of choice due to its low cost and other advantages it offers in terms of selectivity, sensitivity and response time. Detection of Ca^{2+} in the presence of other similar ions like Na^+ , K^+ , Mg^{2+} and Sr^{2+} is a challenging task due to their similar size and properties [14-16, 27-30].

A large number of active compounds, for example, α -furildioxime [31], p-isopropylcalix[6]arene [32], simple ester [33], poly(3,4-ethylenedioxythiophene) [34], polyaniline functionalized with Bis [4-(1,1,3,3-tetramethylbutyl)phenyl]-phosphate [35], polyaniline and (2-ethylhexyl)phosphate [36, 37], poly(3-octylthiophene) [38], poly(3,4-ethylenedioxythiophene) [39] have been explored as ionophores for the construction of ion-selective sensors for Ca^{2+} ions.

We have been working with phenyl ether based compounds for the detection of various metal ions because it offers advantages in terms of rigidity of the phenyl ring and flexibility due to the

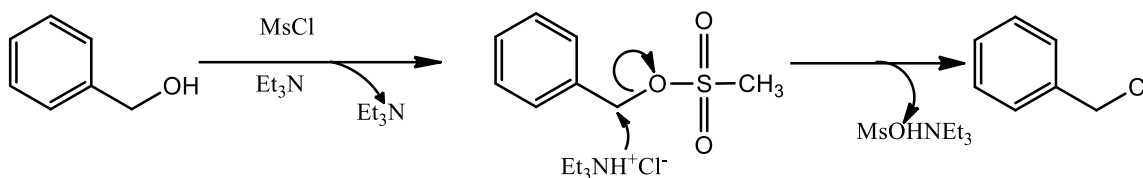
ether linkage [40, 41]. Besides that, placing an appropriate substituent at rest of ten available positions of the phenyl ring offers the benefit of obtaining tunable cavity size.



4b.2 Synthesis

Ionophores **TPE-I**, **TPE-II** and **TPE-III** were synthesized (**Scheme 1**) by slight modification of a previously reported method [42]. The first step involved a reaction of commercially available 1-fluoro-2-nitrobenzene and 3-methoxy-4-hydroxy benzaldehyde in DMF in the presence of K_2CO_3 and 18-crown-6 at room temperature to afford diphenylether DPE-I via nucleophilic aromatic substitution. The deprotection of the methoxy group on DPE-I with aqueous HBr (48 %) and acetic acid gave corresponding phenolic compound that after neutralization was used as such for the next reaction. This required harsher conditions as compared to the initial step due to formation of second ether linkage at sterically hindered ortho position of DPE-I. Therefore, the demethylated product of the compound DPE-I and 1-fluoro-2-nitrobenzene were heated under reflux in DMF using K_2CO_3 and 18-crown-6 to get the desired compound **TPE-I**. Aldehydic group of **TPE-I** was reduced using NaBH_4 and methanol to afford the corresponding hydroxy methyl derivative **TPE-II**. Further, mesityl chloride in the presence of an organic base was preferred as the chlorinating agent to convert **TPE-II** into corresponding chloromethyl product **TPE-III** over the traditional methods that often requires strongly acidic reagents as well as harsh reaction conditions [43-47]. The formation of corresponding mesylate was inhibited by keeping

the reaction at the normal room temperature as well as by longer reaction time. TLC monitoring showed that mesylation preceded chlorination. Following could be the possible reaction pathway



Scheme 4b.2 Possible mechanism for the formation of chloromethyl product using mesityl chloride

All the compounds were characterized by ^1H NMR, ^{13}C NMR and mass spectroscopy techniques. Further investigations for binding with different metal ions were done by potentiometric studies, theoretical studies and UV-Vis. spectroscopy.

4b.3 Absorption studies

To explore the binding efficiency of ionophores towards different metal ions, UV-Vis absorption studies were carried out. The UV-Vis spectroscopic studies of compound **TPE-I** (15 μM) were performed in acetonitrile – water medium (10 mMHEPES in CH_3CN : H_2O 8:2, v/v) at pH 7.0 ± 0.1 . It showed an absorption band at 256 nm due to $n \rightarrow \pi^*$ excitations involving aldehyde group. A comparatively weak transition due to $n \rightarrow \pi^*$ excitations was observed at 290 nm due to nitro groups [48]. On the addition of different metal ions Na^+ , Co^{2+} , Al^{3+} , Sr^{2+} , K^+ , Cu^{2+} , Ni^{2+} , Zn^{2+} , Ba^{2+} , Mg^{2+} , Fe^{2+} and Ca^{2+} (15 μM) to a solution of **TPE-I** in acetonitrile – water medium, no significant changes in the UV-Vis spectra were observed except in the case of Ca^{2+} (Figure 4b.1).

TPE-I showed high selectivity for Ca^{2+} over all other metal ions. A new band was observed in the UV-Visible spectrum at 356 nm on addition of Ca^{2+} ions with simultaneous disappearance of the peak at 256 nm. An increase in the intensity of band at 303 nm was also observed. This indicated complexation of ionophore with calcium ions. Experiments with other metal ions in the

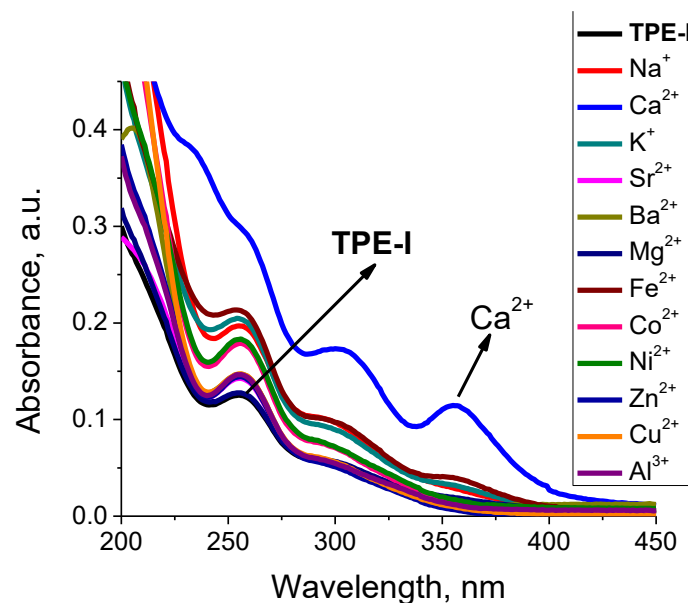


Figure 4b.1 UV – Vis. absorption spectra of **TPE-I** (15 μM) in the presence of metal ions (15 μM) in $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (8:2 ; v/v) at $\text{pH } 7.0 \pm 0.1$ (10 mM HEPES)

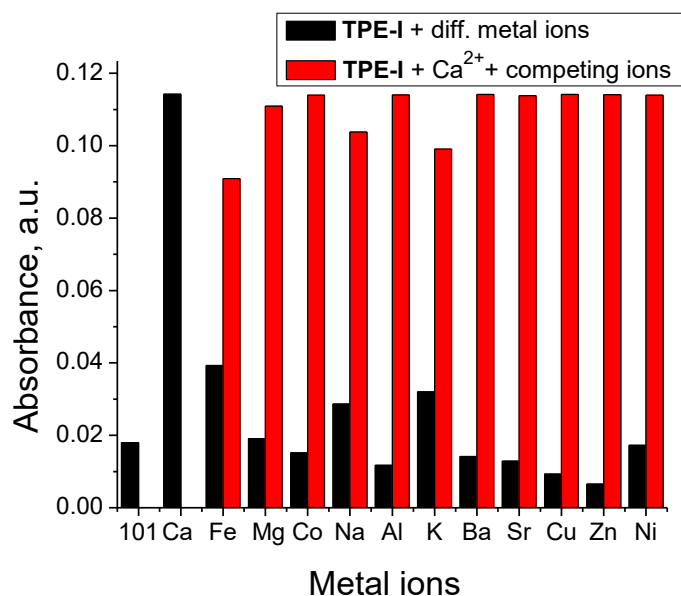


Figure 4b.2 Selectivity of **TPE-I** (15 μM) for Ca^{2+} ions in the presence of other competitive metal ions. Black bars indicate absorbance at 356 nm after the addition of 15 μM of the particular metal ion in a 15 μM solution of **TPE-I**. Red bars represent the subsequent addition of same equivalents of Ca^{2+} ions in each of the samples

presence of Ca^{2+} ion (15 μM) gave no interference in the absorption (Figure 4b.2). Sensitivity of **TPE-I** for calcium ions was examined by titrating different concentrations of calcium ions (0.0 –

2.0 equiv.) in acetonitrile – water medium (Figure 4b.3). Successive additions of Ca^{2+} to the solution of **TPE-I** quenched the absorption band at 256 nm and bands at 303 and 356 nm showed increase in the absorbance. Optical density at 303 nm and 356 nm reached a saturation point at 2 equivalents of calcium ions. The calibration curve drawn between absorbance changes at 356 nm against different concentrations of Ca^{2+} ions showed a linear behavior in the concentration range from $2 \times 10^{-6} \text{ mol L}^{-1}$ to $5.0 \times 10^{-5} \text{ mol L}^{-1}$ with a lower detection limit of $3.0 \times 10^{-6} \text{ mol L}^{-1}$.

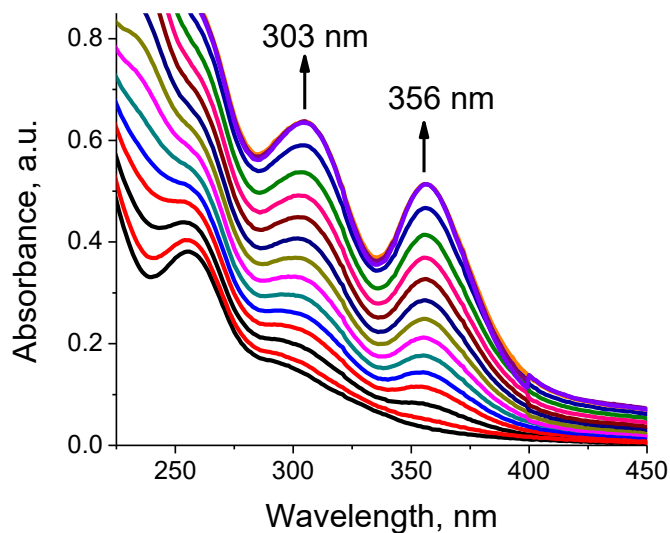


Figure 4b.3 UV–Vis. absorption spectra of **TPE-I** (25 μM) in the presence of different concentrations of Ca^{2+} ions (0.04 – 2.0 equivalents)

Stoichiometry of the Ca(II) complex formed with **TPE-I** was determined by the method of continuous variation (Job's method). Stock solutions (15 μM) of both **TPE-I** and of Ca^{2+} were prepared in acetonitrile – water medium. These stock solutions were used to prepare nine test solutions in a way so as to keep total concentration of receptor **TPE-I** + Ca^{2+} constant at 15 μM . The absorbance of these test solutions were recorded at 356 nm. The parameter used was the absorbance changes at 356 nm, which was calculated according to the following equation:

$$\Delta A = |A - (1 - x_M) \times A_R^\circ - x_M \times A_M^\circ|,$$

Where, x_M is the mole fraction of the metal salt, A_R° and A_M° are the absorbances of the solutions of the receptor and metal salt solutions, respectively. The absorbance changes were plotted against the mole fraction of **TPE-I**. The concentration of complex approached a maximum when

the mole fraction of **TPE-I** was 0.5, which indicated that, **TPE-I** formed a 1:1 complex with Ca^{2+} (Figure 4b.4).

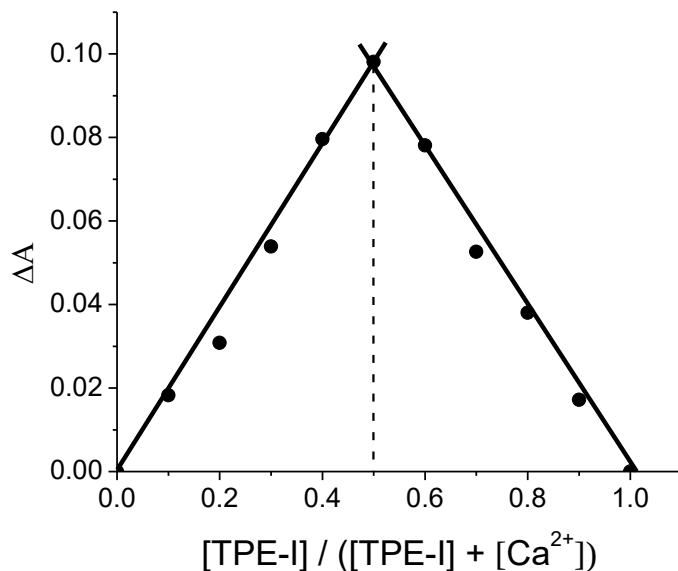


Figure 4b.4 Job's plot of **TPE-I** with Ca^{2+} . Total concentration of **TPE-I** + Ca^{2+} was kept constant at 15 μM

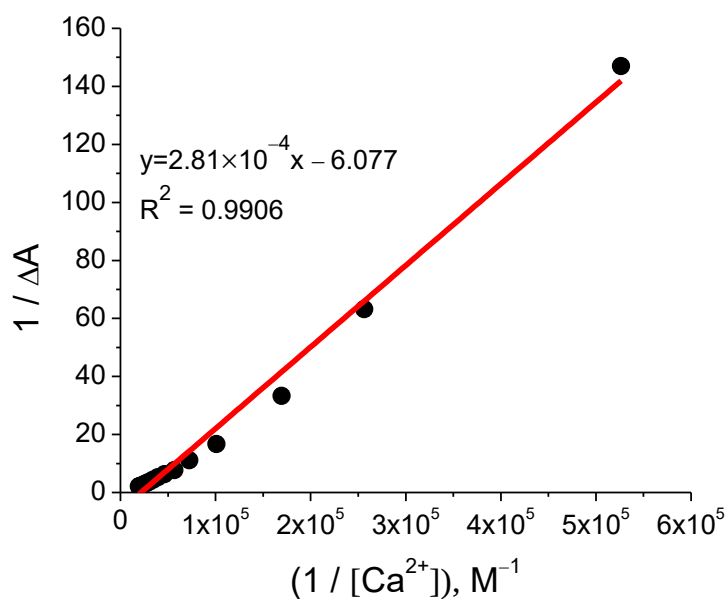


Figure 4b. 5 Benesi – Hildebrand plot of **TPE-I** with Ca^{2+} . The monitored wavelength was 356 nm and the binding constant was $2.1 \times 10^4 \text{ M}^{-1}$

Further support of the 1:1 binding ratio comes from the Benesi- Hildebrand plot, where, the measured absorbance value $1/\Delta A$ at 356 nm varied as a function of $1/[Ca^{2+}]$ in a good linear relationship, which was also an indication of the 1:1 association of the ionophore and Ca^{2+} ions. The association constant given by the slope of the straight line (Benesi-Hildebrand method) was $2.1 \times 10^4 M^{-1}$ in acetonitrile – water medium (Figure 4b.5). ^1H NMR provided further evidence to prove the interaction of ionophore **TPE-I** with Ca^{2+} ions. Titration was done to observe changes in ^1H NMR of the ionophore **TPE-I** with the addition of Ca^{2+} ions in DMSO solution. Protons were observed to shift upfield on addition of 0.5 and 1.0 equivalent of Ca^{2+} ions (Figure 4b.6) in 25 mM solution of the ionophore as compared to its blank. The up field shift and the broadening of ^1H NMR signals confirmed interaction of **TPE-I** with Ca^{2+} ions.

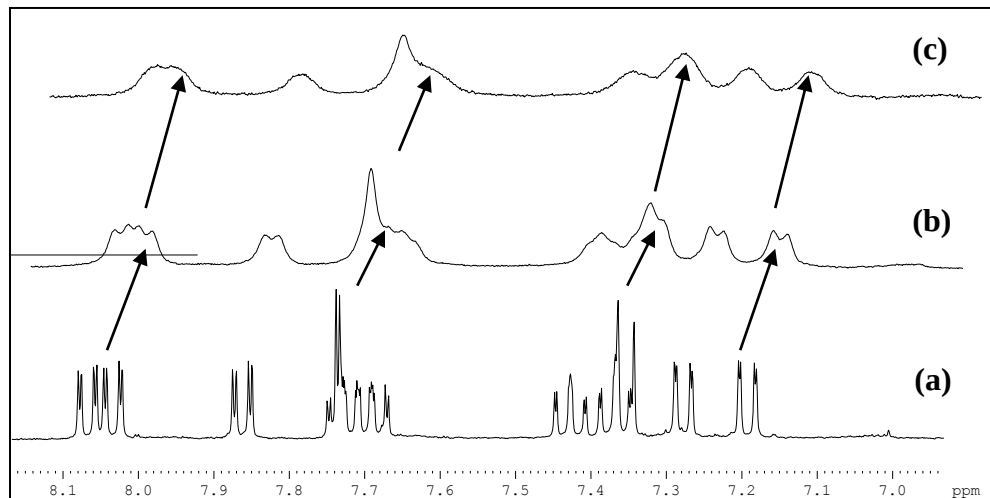


Figure 4b.6 ^1H NMR (400MHz, DMSO) spectra of **TPE-I** (25 mM) upon titration with (a) 0 equiv. (b) 0.5 equiv. (c) 1.0 equiv of Ca^{2+} .

Ionophores **TPE-II** and **TPE-III** also showed similar behavior towards different metal ions i.e. no significant changes in their UV-Vis spectra were observed except in the case of Ca^{2+} . However, significant changes were observed during their interaction with Ca^{2+} . It was reasoned that replacing aldehyde with hydroxy methyl group in **TPE-II** and chloromethyl group in **TPE-III** should produce a corresponding difference in the absorption spectra. Figure 4b.7 shows a shoulder at 257 nm and a weak hump at 270 nm in case of hydroxy methyl (**TPE-II**) and chloromethyl (**TPE-III**) groups, respectively, as compared to aldehyde in case of **TPE-I**.

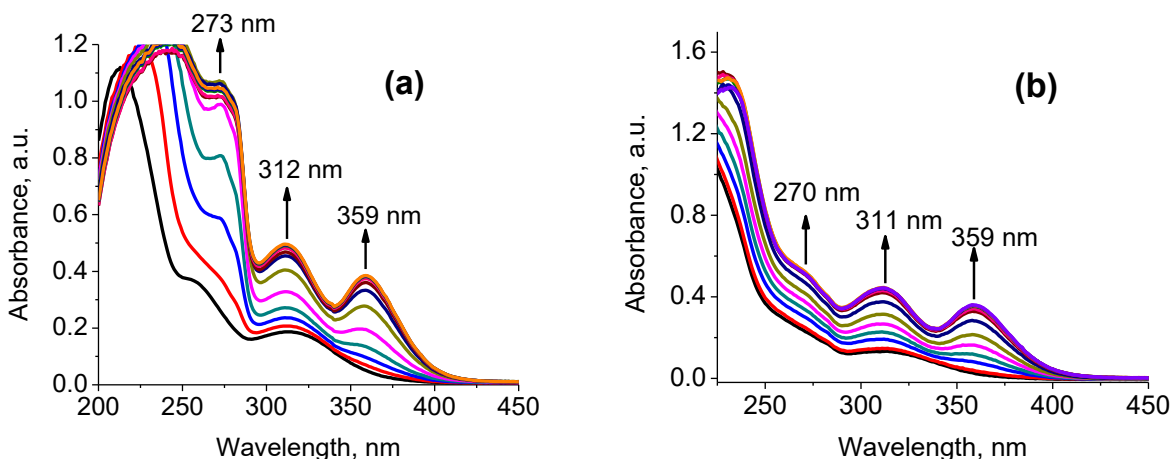


Figure 4b.7 UV–Vis. absorption spectra of **(a) TPE-II** (25 μM) **(b) TPE-III** (25 μM) at pH 7.0 ± 0.1 (10 mM HEPES in $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 8:2, v/v) in the presence of various equivalents of Ca^{2+} (0.02 – 2 equiv.)

This was consistent with the weak n to π^* transition in case of hydroxy and chloro- substituents. The solvent system used in both the cases was acetonitrile – water. There was negligible change in position of the other two transitions at 303 nm and 356 nm confirming that mode of binding in both the cases is same as that in **TPE-I**. Figure 4b.8 shows Benesi- Hildebrand plots of **TPE-II** and **TPE-III**, respectively. The association constants calculated from the slope of these plots are $3.1 \times 10^4 \text{ M}^{-1}$ and $1.6 \times 10^4 \text{ M}^{-1}$ for **TPE-II** and **TPE-III**, respectively.

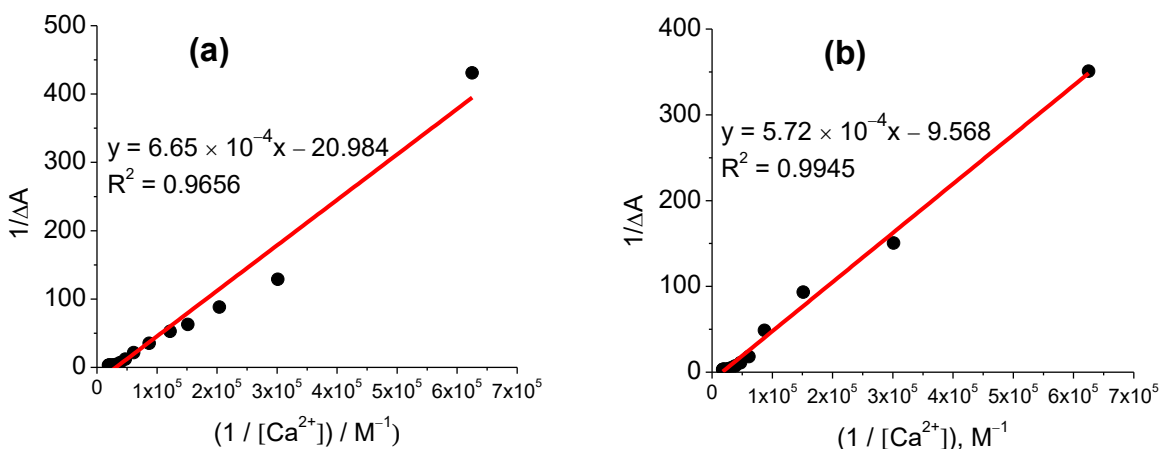


Figure 4b.8 Benesi – Hildebrand plot of **(a) TPE-II** **(b) TPE-III** with Ca^{2+} . The monitored wavelength was 359 nm and the binding constant was 3.16×10^4 and $1.67 \times 10^4 \text{ M}^{-1}$ respectively

Table 4b.1 shows association constants and detection limits for the three ionophores. A comparison of the association constant values indicate that the affinity of Ca^{2+} towards the three triphenyl ethers is: **TPE-II**>**TPE-I**>**TPE-III**. Smaller value of association constant in **TPE-I** than in **TPE-II** could be attributed to the electron deficient carbonyl carbon of $-\text{CHO}$ group, which will reduce the electron density at the ether oxygen atoms, thus weakening the Ca^{2+} binding. Whereas, the electron donating inductive effect of $-\text{CH}_2\text{OH}$ group increases the electron density at the ether oxygen atoms, thus making the pseudo cavity electron richer with stronger affinity to host the metal ion. Smallest value of association constant observed in **TPE-III** is also in accordance to electron withdrawing effect of chloromethyl group.

Table 4b.1 Comparison of some parameters of Ionophores in the presence of Calcium ions in HEPES buffered $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ 8:2, v/v at $\text{pH } 7.0 \pm 0.1$

Ionophore	Stability constant, M^{-1}	Detection limit, mol L^{-1}
TPE-I	2.1×10^4	2.1×10^{-6}
TPE-II	3.1×10^4	5.7×10^{-6}
TPE-III	1.6×10^4	5.4×10^{-6}

4b.4 Quantum chemical calculation

In order to have more insight into geometry of the ionophores and their interaction with metal ions, quantum chemical study was carried out by density functional theory (DFT) method using Gauss View 4.1.2 software. B3LYP method with 6-311G basis set was employed for the optimization of **TPE-I** independently and along with Ca^{2+} , Na^+ , Mg^{2+} and K^+ . Highest energy decrease of 677a.u. was observed for Ca^{2+} , thus, indicating a stable complex formation of **TPE-I** with Ca^{2+} over other metal ions. Na^+ , Mg^{2+} and K^+ showed an energy decrease of 162, 199 and 399 a.u., respectively.

As shown in Figure 4b.9, out of the two nitro groups on the two terminal phenyl rings, one group points away to reduce the steric crowding, and the other nitro group gets involved along with the ether oxygen atoms in constituting the pseudo cavity for the metal ion. Upon addition of Ca^{2+} into this arrangement, a conformational change takes place in which ether group, due to its flexible nature gets rotated and both the nitro groups start participating in coordination to the

Ca^{2+} ion along with two ether oxygen atoms. Also, there was an increase in the stability of whole system, which was confirmed from the value of energy optimization. Binding energies obtained from theoretical studies have proved that energy value for all the three ionophores decreases with the addition of Ca^{2+} as shown in Table 4b.2. This large energy decrease after complexation indicates the formation of stable complexes.

Table 4b.2 Binding energies of different ionophores and their metal complexes calculated at B3LYP-6311G level except for **TPE-III** which was calculated at LAN L2DZ level

Ionophore	Energy (a.u.)
TPE-I	-1367
TPE-I + Ca^{2+}	-2044
TPE-II	-1368
TPE-II + Ca^{2+}	-2045
TPE-III	-1307
TPE-III + Ca^{2+}	-1343

The gap between HOMO – LUMO is less for **TPE-I**- Ca^{2+} complex as compared to ionophore **TPE-I** alone. The frontier molecular orbitals i.e., HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) play an important role in chemical stability and UV-Visible spectra [49, 50]. As shown in Figure 4b.10, the HOMO for ionophore **TPE-I** is distributed over the central phenyl ring containing the aldehyde group as well as on one terminal phenyl ring having nitro group which is participating in forming the pseudo cavity, whereas, the LUMO is distributed over the nitro groups and the other terminal phenyl ring (having nitro group pointing away). In case of **TPE-I** – Ca^{2+} complex, HOMO is mainly distributed on the aldehyde group and LUMO is spread over both the nitro groups as well as terminal phenyl rings, which showed that LUMO is main contributor in electronic transition. Further, the HOMO – LUMO energy gaps for **TPE-I** and its calcium ion complex is equal to 0.1497 a.u. and 0.0811 a.u., respectively. This decrease of energy gap after the complexation is in good agreement both with the bathochromic shift of absorption band at 303 nm as well as increase in intensity at 356 nm, in the presence of Ca^{2+} .

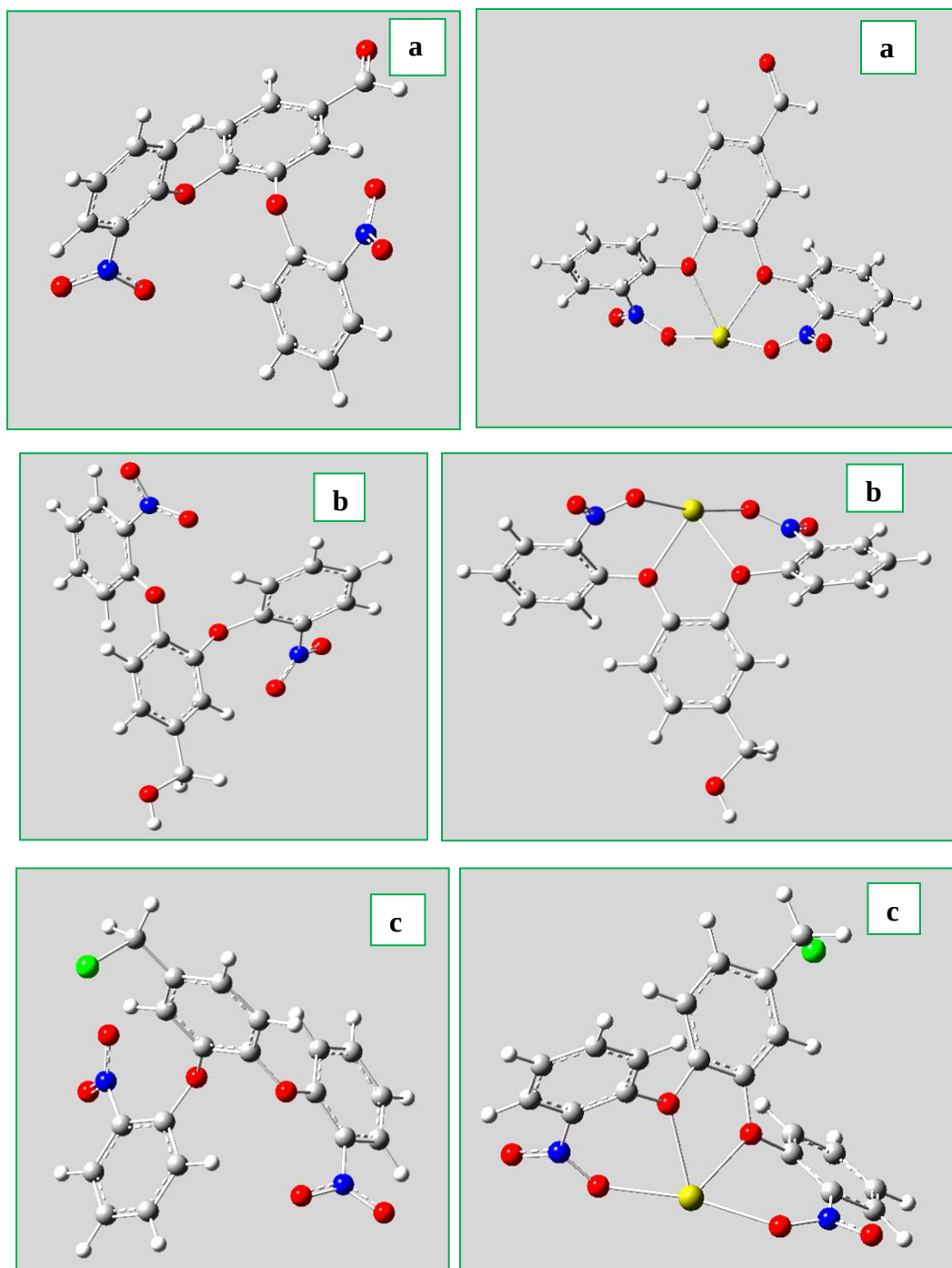
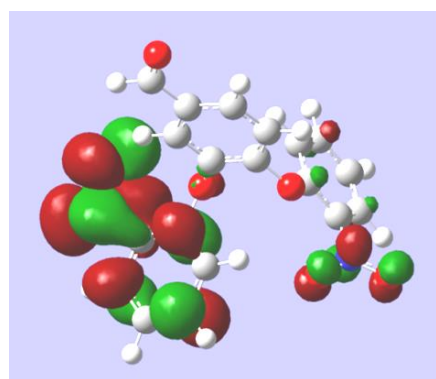
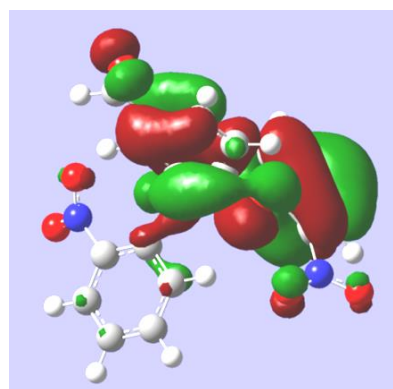


Figure 4b.9 DFT optimized structures of (a) **TPE-I** (b) **TPE-II** (c) **TPE-III** and their Ca^{2+} complexes. White, Red, Blue, Grey, parrot green and green spheres refer to H, O, N, C, Cl and Ca^{2+} , respectively.



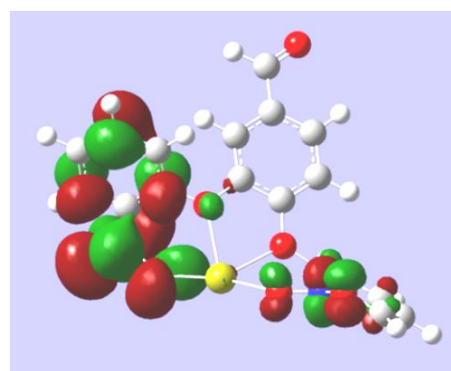
LUMO

0.1497 a.u.



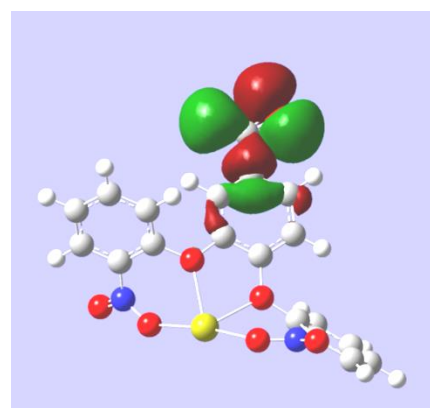
HOMO

(a)



LUMO

0.0811 a.u.



HOMO

(b)

Figure 4b.10 The homo – lumo gap of (a) **TPE-I** and (b) **TPE-I– Ca²⁺** complex calculated at the B3LYP / 6311G level

4b.5 Potentiometric studies

Determination of formation constants

In order to check potentiometric response of the ionophores for a particular metal ion, their interactions with different metal ions were investigated by sandwich membrane method [51, 52]. In this method, the potential of sandwich membranes, E_m were determined by subtracting the cell potential for a membrane without ionophore from that of sandwich membrane for the same electrolyte system. This method allows convenient determination of formation constant of ion-ionophore complexes within the membrane phase on the basis of transient membrane potential measurement on two layer sandwich membranes neglecting the ion pairs. Formation constant values for different metal ions are shown in Table 4b.3 for **TPE-I**, **TPE-II** and **TPE-III**.

Table 4b.3 Formation constants for complexes of ionophores **TPE-I**, **TPE-II** and **TPE-III** with some metal ions using sandwich membrane method

Metal ion		Ca ²⁺	Ba ²⁺	Zn ²⁺	Cu ²⁺	Ni ²⁺	Co ²⁺
Log K _f	TPE-I	6.82	4.81	3.30	4.13	3.76	2.81
	TPE-II	6.99	4.84	3.60	4.32	4.20	2.62
	TPE-III	6.15	4.20	3.21	3.94	3.92	3.11

Effect of the membrane composition on electrode response

In ISEs, the criteria of ionophore selection for a particular ion is based primarily on its Nernstian (linear) response towards the analyte ion in a range of concentrations and further on the slope values. Thus, in preliminary experiments, these ionophores were used as neutral carriers to prepare PVC based membranes for a variety of metal ions and their responses were observed. On the basis of these experiments and formation constant values, three ionophores were found to be highly selective for Ca²⁺ ions over several other metal ions.

The working of the PVC based neutral Carrier membrane electrode is affected strongly by the nature and amount of the ionophore, plasticizer and lipophilic additive used. The additives like anionexcluders enhance the selectivity and sensitivity of cation selective membrane by reducing its resistance [53, 55]. Nature of the plasticizer influences both the dielectric constant as well as mobility of the ionophore and its metal complex [56]. Also, it provides smoothness and flexibility to the membrane and thus enhance the response characteristics [57, 58]. Our

experience of using several plasticizers showed that o-NPOE performs the best when it comes to the case of ions with higher charge density (like Ca^{2+}), because of its high dielectric constant ($\epsilon \approx 21.0$). Thus, o-NPOE was chosen over other less polar plasticizers like AP ($\epsilon \approx 17.1$), DOP ($\epsilon \approx 5.1$) and TEHP ($\epsilon \approx 4.8$). Thus, in order to check the effect of all these components on the selectivity, linearity, slope, detection limit and response time of the electrodes, the amount of ionophore, PVC, o-NPOE and anion excluder (NaTPB) were varied to get the optimum composition. Potential of the membranes (with **TPE-I**, **II** and **III**) for calcium ions were investigated in the range 1.0×10^{-8} to 1.0×10^{-1} M and the results obtained are shown in Table 4b.4. It was observed that in case of **TPE-I** and **TPE-II**, increasing the ionophore content up to 4% improved the electrode response (Fig. 4b.11). However, the electrode containing **TPE-III** shows the best response at 3% ionophore content. Further increase in the ionophore amount in all the three cases resulted either in non – Nernstian slope values or poorer detection limits. This may be due to the reason that equilibration of the ionophores with Ca^{2+} is maximum at this composition.

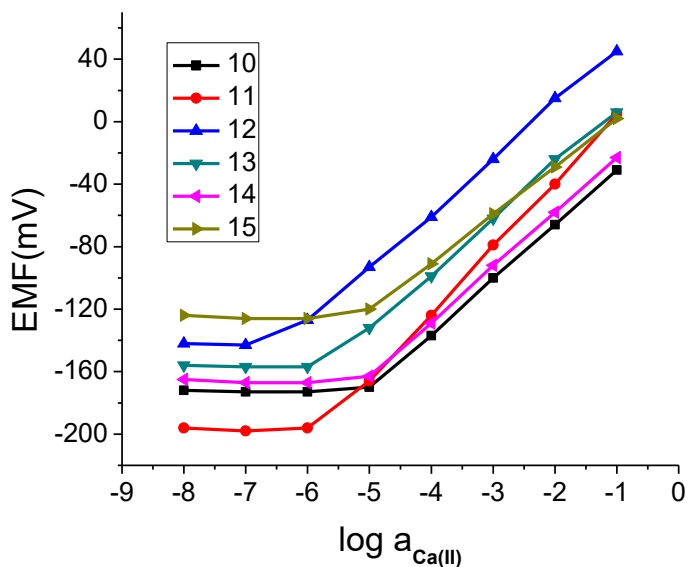


Figure 4b.11 Response of **TPE-II** towards different membrane compositions

Table 4b.4 Optimization of membrane ingredients for Ca²⁺ ISEs

Membrane No.	Ionophore	PVC (Wt%)	Plasticizer (Wt%)	Ionophore (Wt%)	NaTPB (Wt%)	Slope, mV/decade	Detection Limit, (M) (Ca ²⁺)
1	TPE-I	33	63	1	3	16.1	3.2x10 ⁻⁵
2	TPE-I	34	61	2	3	22.1	1.2x10 ⁻⁵
3	TPE-I	33	61	3	3	34.2	8.3x10 ⁻⁷
4	TPE-I	33	60	4	3	28.5	3.6x10⁻⁷
5	TPE-I	32	60	5	3	24.3	1.4x10 ⁻⁶
6	TPE-I	32	59	6	3	18.2	2.5x10 ⁻⁵
7	TPE-I	28	62	7	3	23.1	2.3x10 ⁻⁶
8	TPE-I	33	61	4	2	30.8	7.4x10 ⁻⁷
9	TPE-I	33	59	4	4	24.2	2.6x10 ⁻⁶
10	TPE-II	33	65	2	-----	21.2	1.3x10 ⁻⁵
11	TPE-II	33	61	3	3	30.8	2.1x10 ⁻⁶
12	TPE-II	33	60	4	3	29	3.2x10⁻⁷
13	TPE-II	32	60	5	3	25.2	2.1x10 ⁻⁶
14	TPE-II	32	59	6	3	21.4	1.2x10 ⁻⁵
15	TPE-II	33	60	7	-----	19	9.5x10 ⁻⁶
16	TPE-III	33	65	2	-----	20.2	1.1x10 ⁻⁵
17	TPE-III	33	61	3	3	28	7.9x10⁻⁷
18	TPE-III	33	60	4	3	26.1	6.4x10 ⁻⁷
19	TPE-III	32	60	5	3	20	3x10 ⁻⁶
20	TPE-III	32	59	6	3	18.4	2.1x10 ⁻⁵
21	TPE-III	33	60	7	-----	15	2.5x10 ⁻⁵

Role played by the anionic additive (NaTPB) in the electrode response is clearly visible in the performance of membranes (no. 10, 15, 16 and 21), where a sharp decrease in slope and detection limit is observed primarily because of increased electrical resistance of the membrane in the absence of lipophilic salt. Thus membranes of **TPE-I**, **TPE-II** and **TPE-III** having

compositions of PVC: o-NPOE: ionophore (**TPE-I** / **TPE-II**): NaTPB as 33:60:4:3 wt% (no. 4 and 12) and PVC: o-NPOE: ionophore (**TPE-III**): NaTPB as 33:61:3:3 wt% (no. 17) show the best response, as regards the slope and detection limit. These electrodes were selected for further studies.

Effect of internal solution concentration

Influence of the concentration of internal solution on the emf response of all electrodes was studied [59]. The results showed that a variation in concentration of internal reference solution from 10^{-1}M to 10^{-3}M makes no significant effect on the response of electrodes. However, a 10^{-1}M concentration of internal solution was chosen for further studies.

Effect of non-aqueous medium

Keeping in view that real life samples may contain non-aqueous content, functioning of the best responsive membrane electrodes (no. 4,12 and 17) was also investigated in partially non-aqueous media using 10 to 40% (v/v) non-aqueous content in methanol-water, acetonitrile-water and acetone-water mixtures and results are shown in Table 4b.5.

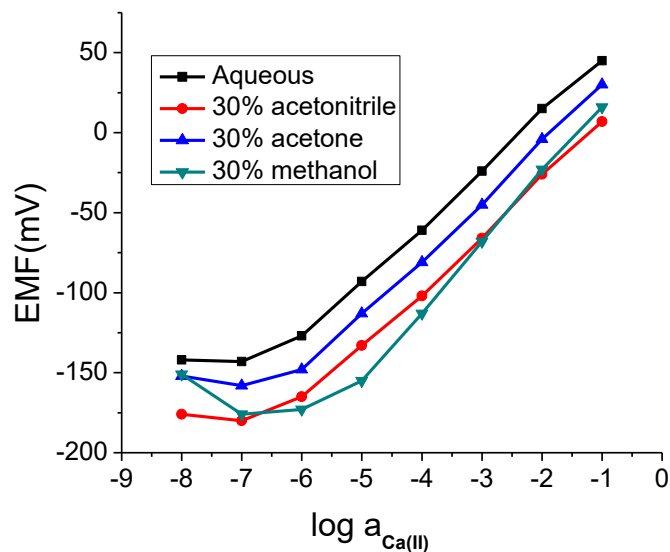


Figure 4b.12 Membrane electrode response of **TPE-II** in different mixed solvent media

It was observed that triphenylether based membrane electrodes worked well up to 20% non-aqueous content without showing any appreciable change in the slope or detection limit. While

Table 4b.5 Response of Ca^{2+} ISEs in mixed solvent media

Solvent	Mixed solvent (%, v/v)	Slope, mV/ decade			Detection limit, M (Ca^{2+})		
		TPE-I	TPE-II	TPE-III	TPE-I	TPE-II	TPE-III
Acetonitrile	10	28.5	29	28	3.6×10^{-7}	3.2×10^{-7}	7.9×10^{-7}
	20	28.5	29	28	3.6×10^{-7}	3.2×10^{-7}	7.9×10^{-7}
	30	28.2	28.3	27.2	3.6×10^{-7}	4.1×10^{-7}	8.9×10^{-7}
	40	26.8	27.3	26.7	1.9×10^{-6}	2.5×10^{-6}	2.3×10^{-6}
Acetone	10	28.5	29	28	3.6×10^{-7}	3.2×10^{-7}	7.9×10^{-7}
	20	28.5	29	28	3.6×10^{-7}	3.2×10^{-7}	7.9×10^{-7}
	30	28.1	28.4	27.1	3.2×10^{-6}	7.4×10^{-7}	2.5×10^{-6}
	40	26.5	27.1	26.3	2.1×10^{-6}	2.6×10^{-6}	2.6×10^{-6}
Methanol	10	28.5	29	28	3.6×10^{-7}	3.2×10^{-7}	7.9×10^{-7}
	20	28.5	28.9	28	3.6×10^{-7}	3.2×10^{-7}	7.9×10^{-7}
	30	27.4	27.2	26.2	2.5×10^{-6}	3.8×10^{-6}	8.3×10^{-6}
	40	26.1	26	23.6	2.3×10^{-5}	2×10^{-5}	1.6×10^{-5}

increasing the non-aqueous content to 30%, acetone and acetonitrile media slightly affected these parameters with methanol showing a comparatively larger variation, particularly in the case of **TPE-II** (no. 12), as shown in Fig.4b.12. This deviation becomes even stronger at 40%, with an appreciable decrease in the detection limit as well as slope. Therefore, these electrodes can be safely used upto 20% non-aqueous content without any drift and up to 30% acetonitrile-water with mild variations. The stronger effect observed in case of **TPE-II** in methanol could be attributed to its $-\text{CH}_2\text{OH}$ group which makes it more soluble in polar methanol medium (due to hydrogen bonding) and hence leads to the leaching of ionophore from the membrane phase.

Effect of substituents on calibration characteristics, response time and life time

Calibration curves were drawn for all the electrodes (membrane no. 4,12 and 17 for **TPE-I**, **TPE-II** and **TPE-III**, respectively) (Figure 4b.13) over a concentration range from 10^{-8} M to 10^{-1} M with an internal filling solution of 10^{-1} M of calcium ions.

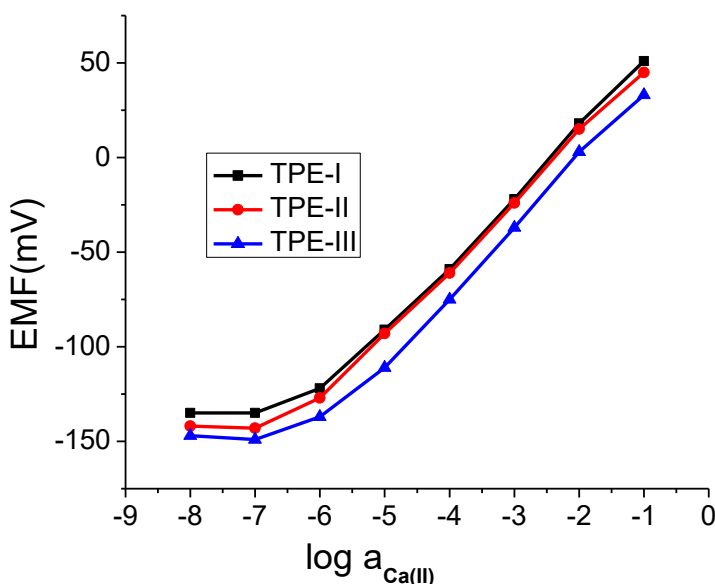


Figure 4b.13 Potentiometric calibration curves for Ca^{2+} selective electrodes based on membrane electrode nos. 4 (**TPE-I**), 12 (**TPE-II**) and 17 (**TPE-III**)

As shown in Table 4b.4, the electrodes (4, 12 and 17) showed near Nernstian reproducible slopes. For five repeated measurements, the standard deviations of the slopes were approximately ± 0.5 mV. The workable concentration range was found to be approximately 10^{-6}

M to 10^{-1} M of Ca^{2+} . However, the detection limits, as calculated according to IUPAC recommendation [60], are 3.6×10^{-7} M, 3.2×10^{-7} M and 7.9×10^{-7} M of Ca^{2+} , respectively for **TPE-I**, **TPE-II** and **TPE-III**. The response time is an important factor for an ISE. In this study the response time was recorded by changing the concentration of metal ion test solution from 1×10^{-6} M to 1×10^{-1} M. The average time required for the electrodes to reach a potential response within ± 1 mV of the final equilibrium value after successive immersion in a series of corresponding metal ion solutions, each having a 10-fold difference in concentration was 15 seconds for **TPE-I**, **TPE-II** and **TPE-III** (no. 4,12 and 17). The potentials remained constant for about 10 minutes after which a very slow divergence was recorded. The membrane electrodes could be used for at least 4 months without any measurable drift in working concentration range, detection limit and slopes. After this period, the electrodes behavior gradually decreased. Electrodes were stored in 0.1 M metal ion solution when not in use to avoid any change in the concentration of ions in the membrane phase.

The changes in terms of sensitivity observed in these acyclic aryether based ionophores could be attributed to the presence of different substituents, which can alter the electronic environment around the ether oxygens of aryether moiety. The improvements observed in slope and detection limit values of the hydroxymethyl derivative **TPE-II** over their corresponding aldehydic and chloromethyl counterparts **TPE-I** and **TPE-III** could be assigned to the replacement of electron withdrawing $-\text{CHO}$ group in **TPE-I** and $-\text{CH}_2\text{Cl}$ group in **TPE-III** by $-\text{CH}_2\text{OH}$ group in **TPE-II**. This will obviously result in an increase of electron density at ethereal oxygens thus improving the ionophoric character of these electrodes.

Potentiometric selectivity

Selectivity behavior is perhaps the single most important characteristic of an ISE, which reflects the nature of device and the extent to which it may be applied in the determination of a particular ion in the presence of other interfering ions. This is measured in terms of potentiometric selectivity coefficients, which were determined using the IUPAC recommended Fixed Interference Method (FIM). In this method, a fixed concentration of interfering ions (1.0×10^{-2} M) and a varying concentration of calcium ion solution ranging from 1×10^{-1} M to 1×10^{-8} M was used. The potentiometric selectivity coefficients were then determined using the following expression [61]:

$$K_{AB}^{POT} = \frac{a_A}{a_B^{z_A/z_B}}$$

Where, a_A is activity of the primary ion A at the lower detection limit in the presence of interfering ion B, a_B , the activity of interfering ion B and z_A and z_B are their respective charges. The values of selectivity coefficients determined are shown in Table 4b.6.

Table 4b.6 Potentiometric selectivity coefficients of Ca^{2+} ISEs by Fixed interference method

Interfering ions	$\log K_{\text{Ca}^{2+}, \text{B}}$		
	TPE-I	TPE-II	TPE-III
Sr^{2+}	-0.4	-0.5	-0.4
Ba^{2+}	-1.2	-1.3	-1.1
Ni^{2+}	-1.8	-1.8	-1.6
Cu^{2+}	-1.7	-1.7	-1.5
Na^+	-1.1	-1.1	-1.1
Zn^{2+}	-2.1	-2.2	-2.1
Co^{2+}	-2.4	-2.5	-2.4
Mg^{2+}	-1.9	-2.1	-1.8
K^+	-1.3	-1.3	-1.3
Mn^{2+}	-2.1	-2.4	-2
Fe^{2+}	-1.3	-1.5	-1.3

Table reveals that all the electrodes are highly selective towards Ca^{2+} over a number of monovalent and divalent cations. However, Sr^{2+} may cause some interference as selectivity coefficient values are slightly higher for this ion. Thus, to have a clear picture of the interference caused by Sr^{2+} ions, some mixed run studies were carried out [62] using Ca^{2+} selective electrode **TPE-II** (membrane no. 12). Sr^{2+} ions in the concentration $\leq 1 \times 10^{-6}\text{M}$ do not cause any significant deviation in the plot of pure Ca^{2+} solution. Thus, the electrode can tolerate Sr^{2+} up to

this concentration over the entire working concentration range. If Sr^{2+} concentration exceeds this limit, the sensor can be used to determine Ca^{2+} over the reduced concentration ranges only. Figure 4b.14 shows that in the presence of 1×10^{-5} M, 1×10^{-4} M, 1×10^{-3} M Sr^{2+} ions, the electrode assembly can be used to determine Ca^{2+} in the concentration ranges 3.1×10^{-6} to 1×10^{-1} , 3.1×10^{-5} to 1×10^{-1} and 3.9×10^{-4} to 1×10^{-1} M, respectively.

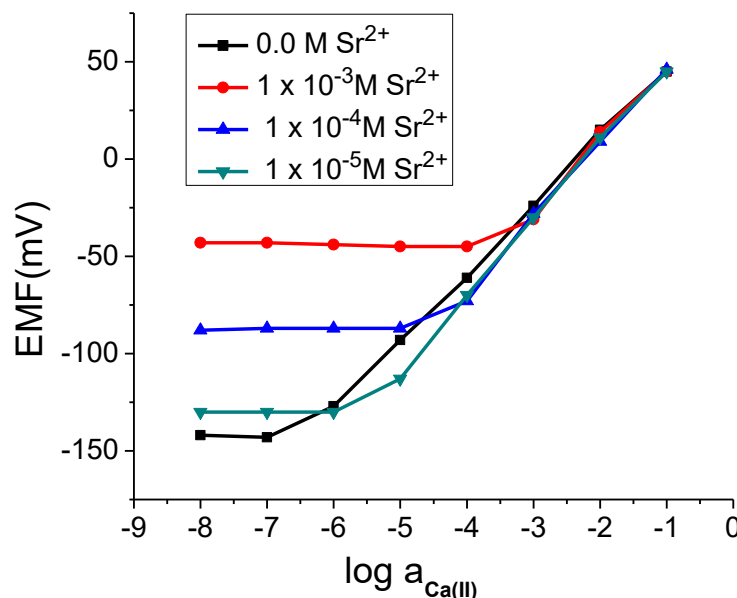


Figure 4b.14 Variation of potential of membrane no. 12 (**TPE-II**) with Ca^{2+} activity in the presence of different concentrations of Sr^{2+} ions

Effect of pH on performance of ISE

The influence of the pH on the response of the membrane electrodes (no.4,12 and 17 for **TPE-I**, **TPE-II** and **TPE-III**, respectively) was examined by measuring their potentiometric responses at 10^{-3} M concentration of calcium ions with solutions of different pH values ranging from 1 to 12. The pH was adjusted by adding small amounts of HCl (0.1 M) or NaOH (0.1 M), as per requirement and results are shown in Figure 4b.15. The emf is independent of pH in the range of 4 – 9 for **TPE-I** and **TPE-III** while for **TPE-II** the pH range with stable potential was approximately 4 – 10. The variations above this pH range may be assigned to the formation of metal hydroxides and below this range due to the H^+ co-fluxing.

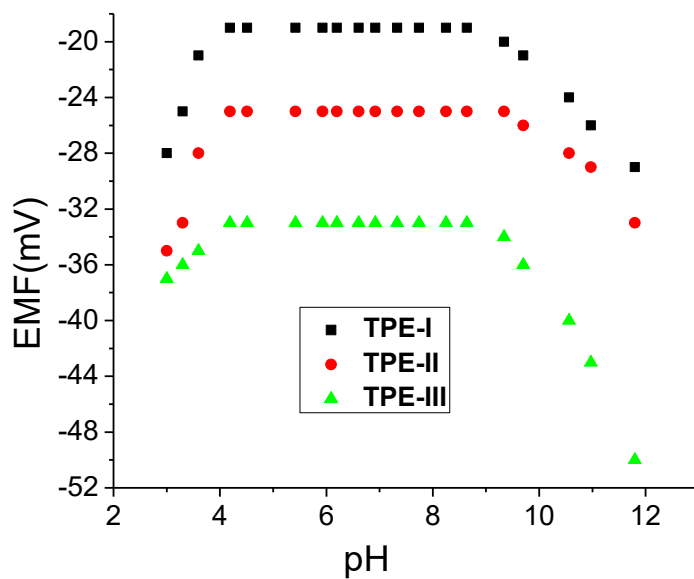


Figure 4b.15 Effect of pH at 1×10^{-3} M Ca^{2+} solution on the potential response of Ca^{2+} ISEs

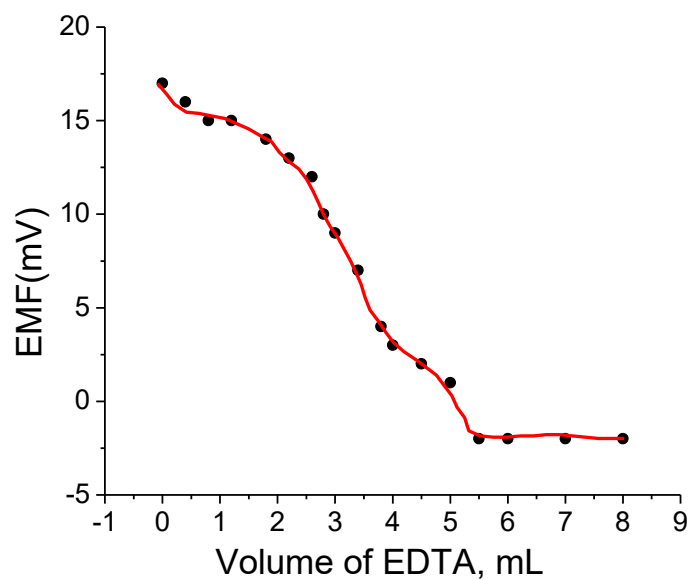


Figure 4b.16 Potentiometric titration of Ca(II) (25 mL of 1×10^{-2} M) with EDTA (1×10^{-1} M) using Ca(II) selective electrode based on **TPE-II**

Applications of ISE

The electrodes have been applied successfully for the end point determination of Ca^{2+} in the potentiometric titration. Potentiometric titrations were performed by using the proposed electrodes as indicator electrode for the titration of 25 mL of 1×10^{-2} M Ca^{2+} against 1×10^{-1} M solution of EDTA. The titration curve for **TPE-II** is shown in Figure 4b.16. The titration curve shows sharp inflexion point corresponding to 1:1 stoichiometry of the complex. Therefore, the proposed membrane electrode can be used as indicator electrode for the determination of Ca^{2+} in potentiometric titrations against complexing agents like EDTA.

Table 4b.7 Comparison of Ca^{+2} selective electrodes with the reported electrodes

S. no	Ionophore	Working Conc.Range (M)	Detection limit (M)	pH Range	Slope (mV/decade)	Reference
1	α -furildioxime	2.5×10^{-7} - 1.0×10^{-1}	-	3.5 - 9.0	29.5	31
2	<i>p</i> -isopropylcalix[6]arene	3.9×10^{-6} – 1×10^{-1}	-	2.5 - 6.0	30.0	32
3	Simple Ester	1.0×10^{-4} - 1.0×10^{-1}	-	3.4 - 6.2	21.0	33
4	poly(3,4-ethylenedioxythiophene)	10^{-5} - 10^{-1}	1.0×10^{-5}	-	28.6	34
5	bis[4-(1,1,3,3-tetramethylbutyl)phenyl]-phosphate	10^{-1} - 10^{-4}	8×10^{-7}	-	27.8	35
6	Polyaniline and di(2-ethylhexyl)phosphate	10^{-1} - 10^{-3}	10^{-4}	-	27.0	36
7	polyaniline and di(2-ethylhexyl)phosphate	10^{-3} - 10^{-1}	5×10^{-3}	-	28.6	37
8	poly(3-octylthiophene)	10^{-7} - 10^{-1}	6×10^{-7}	-	30.0	38
9	poly(3,4-ethylenedioxythiophene)	10^{-4} - 10^{-1}	5.0×10^{-4}	-	27.3	39
10	*Proposed ionophore	10^{-7} - 10^{-1}	3.2×10^{-7}	4.0 - 10.0	29.0	-----

4b.6 References

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ACYCLIC ARYLAMINES AS ION SELECTIVE ELECTRODES

4c.1 Introduction

The design and synthesis of artificial ionophores for selective cation recognition is a field of significant interest, as cations play a key role in major biological and chemical processes [1, 2]. Complimentarily i.e., the size fit requirement and preorganization are the two major attributes that must be designed into an ionophore in order to achieve high selectivity for a particular guest. Further, the affinity for metal cations is also regulated by the character of the donor atoms contained in the ionophore framework [3, 4]. While the hard electron donor nature of oxygen atoms, favour the formation of complexes with alkali and alkaline earth metal cations, incorporation of nitrogen donor atoms is attractive, as it alters the binding tendency of ionophores so that they may complex more readily the cations of transition metals [5]. Keeing in view the above factors, oxygen atoms of the substituted diphenyl ether moiety were replaced by softer nitrogen atoms and two new ionophores **DPA** and **TPA** were designed and synthesized. Ionophoric potential of these ionophores was explored by potentiometric methods, which offer advantage in terms of sensitivity, selectivity, simplicity, low cost and good precision [6-9]. On the basis of these studies, **DPA** was found to have strong affinity for Zn^{2+} ions, whereas the changed complimentarity due to increased number of donor atoms in **TPA** makes it selective towards Ni^{2+} .

The determination of trace amounts of Zinc and Nickel is of great interest in many fields, including biological studies, medicine analysis and environmental monitoring. Zinc is an essential element for human body and plays an important role in immune functioning, DNA synthesis and the activity of enzymes [10, 11]. Approximately 8 to 15 mg of zinc per day is required to maintain health [12], whereas uptake of zinc beyond a threshold value of 124mg/m^3 could be toxic to human beings and is known to cause renal failure, pulmonary disorders, gastroenteritis, anaemia, fever and internal organ damage. Higher concentrations of zinc may induce the intestinal cells to synthesize a protein that captures copper in a non-absorbable form [13], thus causing copper-deficiency anaemia. Extensive use of zinc in pharmaceutical, electroplating and paint industries is increasing its concentration in water, air and soil [14], thus

making it a pollutant. Higher concentrations of zinc may shrink the microbial activity of the soil resulting in phytotoxic effect [15, 16].

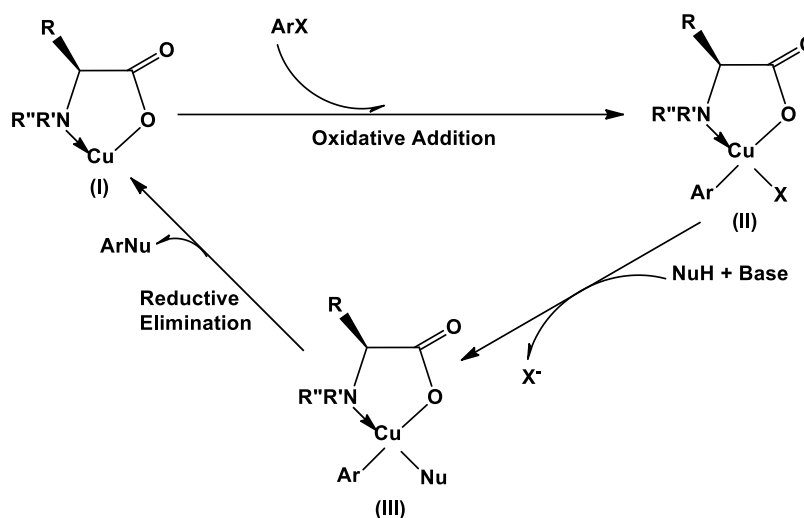
Nickel is found naturally in both food and water and may be increased by human pollution. Monitoring of nickel is also of great importance for biological and environmental studies, since both the deficiency as well as excess of it may prove deleterious to animal and plant systems [17-20]. The tolerable limit of Nickel ions in drinking water is 2.5 mg/ mL [21]. Of course, nickel is not a cumulative poison, but higher doses may be toxic and constitute an occupational hazard. Beyond the threshold limit, nickel is known to cause disorders of central nervous system, asthma, dermatitis and cancer [22].

Various types of analytical techniques such as flame atomic absorption spectrometry, voltammetric methods, atomic emission spectroscopy, UV-Vis spectroscopy etc. have been used for the detection of trace amount of zinc [23-35] and nickel [36-40], but all these methods have various limitations. However potentiometric ISEs due to their simplicity, wide linear range, fast and inexpensive procedure are quite suitable for determination of zinc. A large number of active compounds like [BzO₂Me₂Ph₂(16)hexaeneN₄][41], N,N-bis(2-hydroxy-4-methoxybenzaldehyde)-2,6-diamino pyridine [42], N,N'-phenylenebis (salicylideaminato) [10] , Zn-ATSC [43], PME-6,7:14,15-BzO₂-10,11-(4-methylbenzene)-[15]-6,8,12,14-tetraene-9,12-N₂-1,5-O₂[44], Dibenzo-24-crown-8[45], 1,12,14-Triaza-5,8-dioxo-3(4),9(10)-dibenzoylcyclopentadeca-1,12,14-triene[46], 3-[(2-Furylmethylene)amino]-2-thioxo-1,3-thiazolidin-4-one [47], N,N-Bis(acetylacetone)ethylenediamine [48], Bis(2-nitrophenyl)disulfide [49], Potassiumhydrotris(N-tert-butyl-2-thioimidazolyl)borate [50] have been explored as ionophores for the construction of ion-selective sensors for Zn⁺² ions. Similarly, a number of nickel selective potentiometric sensors based on porphyrins, crown ethers, cyclams, amines and Schiff bases have been investigated [38, 39, 51-57]. In this work, we report the use of two acyclic arylamine based sensors N-(2-nitrophenyl) benzene-1,2-diamine (**DPA**) and N, N-bis(2-nitrophenyl)benzene-1,2-diamine (**TPA**) for preparing highly selective Zn²⁺ and Ni²⁺ membrane electrodes, respectively.

4c.2 Synthesis

Ullmann condensation [58], which involves a copper mediated reaction between an aryl halide and an amine to get the corresponding arylamine is now a well established procedure. Earlier drawbacks of this reaction like high temperature and long reaction times encouraged significant efforts to develop relatively mild reaction conditions [59, 60]. Such efforts resulted in a wide

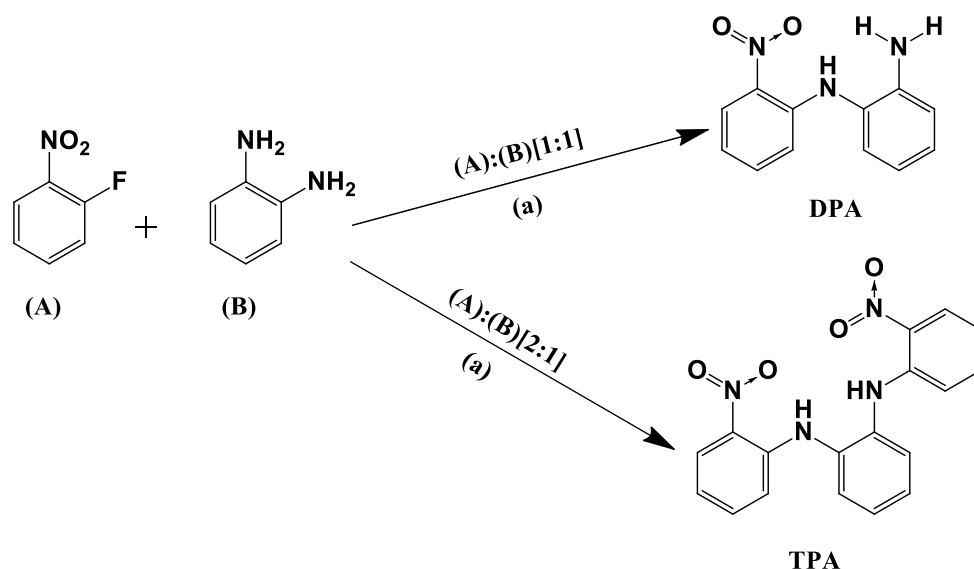
range of new procedures for various applications [61-64] and led to the improved catalytic version of this classical method known as ‘modified Ullmann reaction’. Modified version mainly involves the addition of a bidentate chelator such as amino acids [65-67], diamines [68] or other nitrogen and oxygen containing ligands [69, 70], which improves the efficiency of copper catalyst by increasing its solubility. In case of amino acids, these were secondary and tertiary amino acids such as N-methylglycine, L-proline, and N, N-dimethylglycine, which were selected for the reaction,



Scheme 4c.1 Catalytic cycle for Ullmann coupling reaction with amino acids as ligands

mainly because of their lesser competitive nature towards the reactant amines in coupling with aryl halides. The reaction has been proposed to follow a catalytic cycle (Scheme-1) which involves an oxidative addition and reductive elimination pathway. The chelation of Cu(I) with an α -amino acid makes the Cu(I) species more reactive toward an oxidative addition step or stabilizes the intermediate involved, thus facilitating the coupling reaction.

Using the same methodology, ionophores **DPA** and **TPA** were synthesised (Scheme 4c.2) by nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene (A) with 2-aminophenylamine (B) in a mole ratio of 1:1 and 2:1 respectively. Contents were refluxed for 24-30 hours in an aprotic solvent using K₂CO₃ as base, CuI and amino acid L-Proline as catalysts to afford di and triphenylamines. The two ionophores were then tested for binding with different metal ions by potentiometric and theoretical studies.



Reagents : (a) K_2CO_3 , CuI, Proline, DMSO, 110°C

Scheme 4c.2 Synthesis of Arylamine Ionophores

4c.3 Potentiometric studies

Determination of binding constants of DPA and TPA using sandwich membrane method

The ionophore-complex formation constants were determined potentiometrically. Both the ionophores were separately used to prepare sandwich membranes by mechanically pressing together, the individual membranes; the membrane with ionophore to the membrane without ionophore. Experiments were carried out according to the sandwich membrane method [71, 72]. The formation constants are then calculated according to the following equation.

$$\beta_{Ln} = \left(L_T - \frac{nR_T}{Z_I} \right)^{-n} \exp \left(\frac{E_M Z_I F}{RT} \right)$$

Where, L_T is the total concentration of ionophore in the membrane segment, R_T is the concentration of lipophilic ionic site additives, n is the ion-ionophore complex stoichiometry, R , T and F have the usual meanings and primary ion carries a charge z_i .

The formation constant values are an indication of the binding affinity of different metal ions towards a particular ionophore. The calculated values in case of **DPA** for Fe^{2+} , Co^{2+} , Ca^{2+} , Mn^{2+} , Cu^{2+} and Zn^{2+} are 5.3, 4.7, 4.1, 3.7, 5.8 and 7.4, respectively, which shows that Zn^{2+} ions have

the highest affinity towards this ionophore. Similarly, **TPA** was interacted with Ca^{2+} , Cu^{2+} , Ni^{2+} , Mg^{2+} , Zn^{2+} and Co^{2+} . Formation constant values for different metal ions are shown in Table 4c.1. Highest log K_f values were observed for Ni^{2+} indicating that **TPA** forms most stable complex with Ni^{2+} as compared to other ions.

Table 4c.1 Formation constants for complexes of ionophores **DPA** and **TPA** with some metal ions using sandwich membrane method

DPA		TPA	
Metal Ion	Log K_f	Metal Ion	Log K_f
Zn^{2+}	7.4	Ni^{2+}	8.3
Cu^{2+}	5.8	Cu^{2+}	6.2
Mn^{2+}	3.7	Co^{2+}	3.6
Ca^{2+}	4.1	Mg^{2+}	3.8
Co^{2+}	4.7	Ca^{2+}	3.4
Fe^{2+}	5.3	Zn^{2+}	4.8

Optimization of membrane ingredients and effect of ionophore concentration

Based on formation constant values and preliminary experiments in which **DPA** and **TPA** based PVC membranes were tested for a variety of metal ions, it was concluded that **DPA** showed good response towards Zn^{2+} ions and **TPA** towards Ni^{2+} ions (Figure 4c.1). Preferential response towards a particular metal ion is believed to be associated with selective coordination of the ionophore to the respective ion. Although, key ingredient of the membrane is the incorporated carrier which governs the selectivity of the electrode via selective complex formation with the most suitable cation, the sensitivity of the electrode is significantly related to other membrane parameters like amount of ionophore, PVC, plasticizer (o-NPOE) and lipophilic salt [73, 74]. Thus, in order to get the best electrode characteristics, membrane composition was optimized by varying the amount of these ingredients.

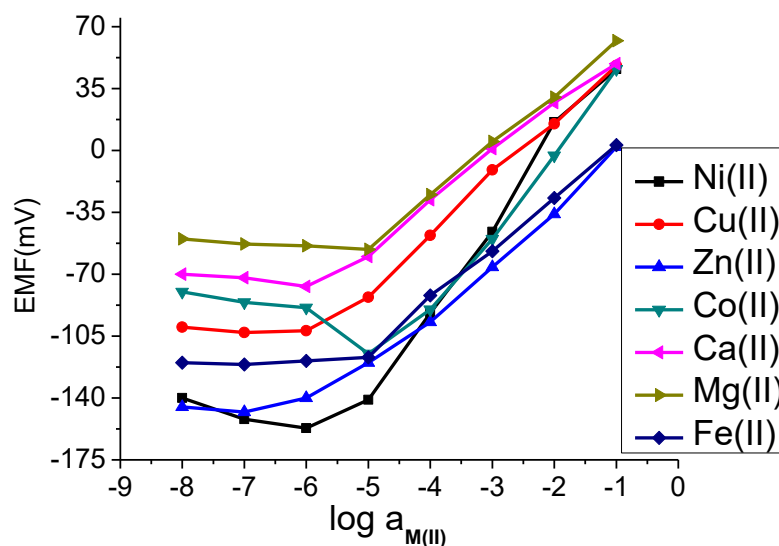


Figure 4c.1 Response of TPA towards different metal ions

Table 4c.2 Optimization of membrane ingredients for Zn^{2+} ISE based on DPA

Membrane No.	PVC (Wt%)	Plasticizer (Wt%)	Ionophore (Wt%)	NaTPB (Wt%)	Slope,mV/decade	Detection Limit,(M) (Zn^{2+})
1	33	63	1	3	20	1.0×10^{-5}
2	33	64	2	1	21	8.2×10^{-5}
3	33	61	3	3	30	1.3×10^{-6}
4	34	61	2	3	21	3.2×10^{-5}
5	33	60	4	3	36	6.3×10^{-5}
6	32	60	5	3	33	1.2×10^{-5}
7	32	59	6	3	20	3.6×10^{-5}

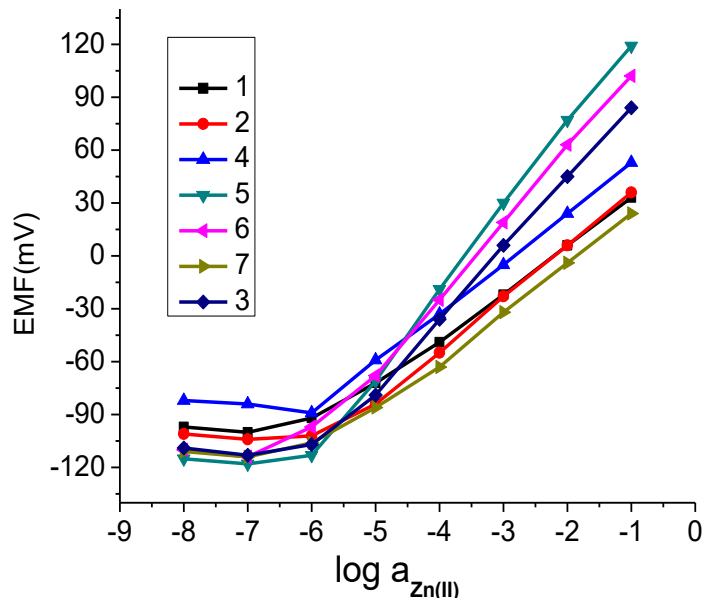


Figure 4c.2 Response of **DPA** for different membrane compositions

Response of Zn^{2+} selective diphenylamine based electrode is shown in Figure 4c.2 and Table 4c.2. The data clearly shows that any change in the **DPA** content less than or greater than 3% leads to non-Nernstian responses. Variation in the o-NPOE and NaTPB amounts also affect the detection limit and slope values. Membrane no. 3 having composition of PVC : o-NPOE : **DPA** : NaTPB as 33:61:3:3 wt% shows the best response in terms of slope and detection limit. This electrode was selected for further studies. Similarly a number of membrane compositions were tried for triphenylamine based Ni^{2+} selective electrode (Table 4c.3). Insignificant selectivity towards Ni^{2+} ions was shown by the blank membranes (i.e. membranes without **TPA**) and their responses were unreliable. A composition with 3% NaTPB as well as 3% **TPA** content showed the best response. Higher or lower amounts than 3% leads to poor electrode responses. Increasing the ionophore content from 1 to 3% and decreasing the plasticizer content accordingly improves the sensitivity of electrode response. Membrane no. 9 having composition of **TPA** : PVC : o-NPOE : NaTPB as 3:32:62:3 (wt%) shows the best response in terms of slope and detection limit. This membrane was selected for further studies.

Table 4c.3 Optimization of membrane ingredients for Ni²⁺ ISE based on **TPA**

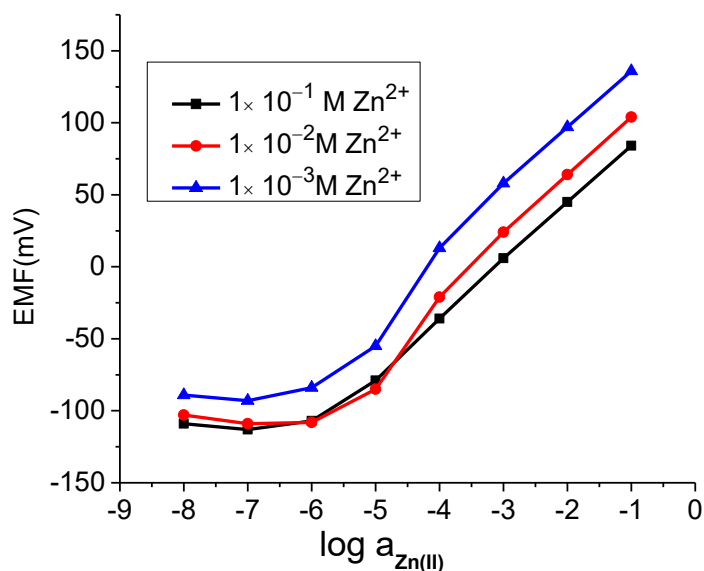
Membrane No.	Ionophore (% w/w)	PVC (% w/w)	NPOE (% w/w)	NaTPB (% w/w)	Slope, mV/decade	DetectionLimit, (M) (Ni ²⁺)
1	–	33	67	–	–	–
2	–	33	65	2	–	–
3	1	33	65	1	14.3	2.4×10 ⁻⁴
4	1	32	65	2	15.2	7.1×10 ⁻⁴
5	2	33	64	1	20.8	6.8×10 ⁻⁴
6	2	32	65	1	19.8	2.7×10 ⁻⁴
7	2	32	64	2	21.2	8.2×10 ⁻⁵
8	2	33	63	2	21.8	7.6×10 ⁻⁵
9	3	32	62	3	30.0	2.5×10⁻⁶
10	3	33	61	3	26.5	9.2×10 ⁻⁶
11	3	33	63	1	25.8	1.2×10 ⁻⁵
12	4	33	60	3	37.0	4.3×10 ⁻⁶
13	4	32	61	3	35.2	3.8×10 ⁻⁵
14	5	32	61	2	34.0	1.2×10 ⁻⁵
15	5	32	60	3	33.2	8.7×10 ⁻⁵

Calibration curve, response time and life time of the electrode

The polymeric membrane electrodes for Zn²⁺ ions and Ni²⁺ ions based on **DPA** and **TPA**, respectively, have been tested according to IUPAC recommendations [75] at different internal reference solution concentrations in the range of 1×10^{-3} to 1×10^{-1} M and response of the electrodes have been observed. As shown in Table 4c.4, **DPA** showed considerable variation in slope values, though not much change was observed in detection limit (Figure 4c.3). It was observed that 1×10^{-1} M concentration of the respective ions gave the best response in both the ionophores and was chosen for further studies.

Table 4c.4 Effect of internal solution concentration on the potential response of **DPA**

Internal solution concentration, M	Slope, mV/ decade	Detection limit, M (Zn ²⁺)
1×10^{-1}	30.0	1.3×10^{-6}
1×10^{-2}	33.0	3.4×10^{-6}
1×10^{-3}	36.0	8.5×10^{-6}

**Figure 4c.3** Effect of internal solution concentration on the potential response of **DPA**

Calibration curve for the Zn²⁺ selective **DPA** based electrode was drawn for membrane no. 3 (Table 4c.2) over a concentration range from 10^{-8} M to 10^{-1} M with an internal filling solution of 10^{-1} M of Zn²⁺ ions, as shown in Figure 4c.4. Emf of the membrane electrode shows a linear range from 1×10^{-6} M to 1×10^{-1} M with a Nernstian slope of 30 mV/decade. The detection limit, as calculated according to IUPAC recommendation [76], is 1.3×10^{-6} M of Zn²⁺ ions.

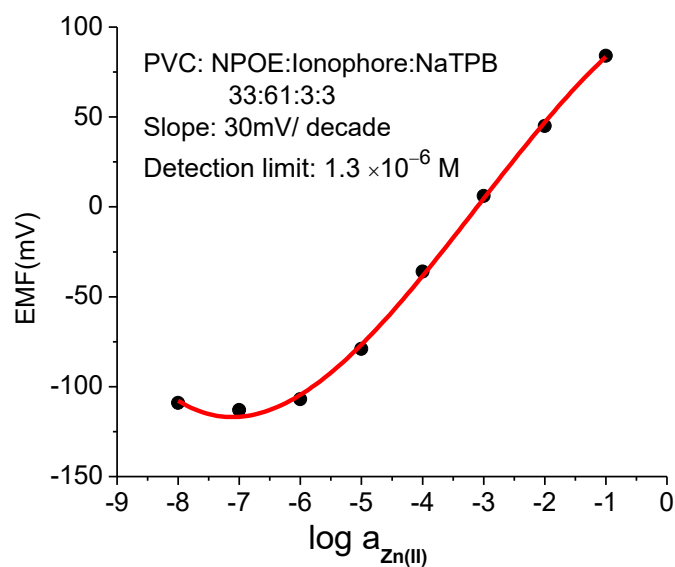


Figure 4c.4 Potentiometric calibration curve for Zn^{2+} selective electrode based on **DPA**

Similarly, for the triphenylamine based Ni^{2+} selective electrode, the best responsive membrane i.e., no. 9 (Table 4c.3) was chosen to draw the calibration curve (Figure 4c.5).

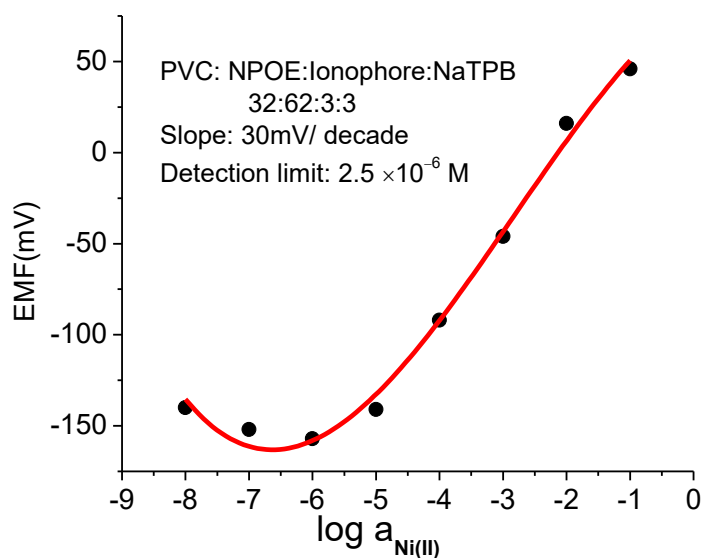


Figure 4c.5 Potentiometric calibration curve for Ni^{2+} selective electrode based on **TPA**

Emf values at varying Ni(II) concentration shows a workable concentration range from 1×10^{-5} M to 1×10^{-1} M with a Nernstian slope of 30 mV/decade. The detection limit is 2.5×10^{-6} M as determined from the intersection of the extrapolated segments of the calibration plot. Similarly, for the **TPA** based Ni^{2+} selective electrode, the best responsive membrane i.e., no. 9 (Table 4c.3) was chosen to draw the calibration curve (Figure 4c.5). Emf values at varying Ni(II) concentration shows a workable concentration range from 1×10^{-5} M to 1×10^{-1} M with a Nernstian slope of 30 mV/decade. The detection limit is 2.5×10^{-6} M as determined from the intersection of the extrapolated segments of the calibration plot. Response time is measured by recording the emf of the electrode as a function of time. It is actually the time taken to attain a response that is within 1mV of the steady-state signal after addition of the ion to the sample. While **DPA** was found to show a stable potential within 15 seconds, nickel selective **TPA** based electrode stabilized in 20 seconds. Both the electrodes could be used for about 4 months without observing any considerable change in the electrode characteristics. **DPA** and **TPA** based membrane electrodes were stored in 0.1 M Zn^{2+} and Ni^{2+} solution, respectively, when not in use.

Table 4c.5 Response of Zn^{2+} ISE based on **DPA** in mixed solvent media

Solvent	Mixed Solvent (%)	Slope, mV/ decade	Detection limit, M (Zn^{2+})
Methanol	10	31.7	3.2×10^{-6}
	20	33.2	6.3×10^{-6}
	30	18.7	$2.1. \times 10^{-5}$
Acetone	10	32.1	5.2×10^{-6}
	20	26.0	8.4×10^{-6}
	30	24.0	7.3×10^{-5}
Acetonitrile	10	31.0	6.3×10^{-6}
	20	34.7	3.1×10^{-6}
	30	19.3	1.0×10^{-5}

Effect of non-aqueous medium

Working of electrodes in non-aqueous medium was tested by observing the response of both electrodes in partially non-aqueous media using 10 to 30% (v/v) non-aqueous content in methanol-water, acetonitrile-water and acetone-water mixtures and results are shown in Table 4c.5 and 4c.6 for Zn^{2+} and Ni^{2+} selective electrodes respectively.

Table 4c.6 Response of Ni^{2+} ISE based on **TPA** in mixed solvent media

Solvent	Mixed Solvent (%)	Slope, mV/ decade	Detection limit, M (Ni^{2+})
Acetonitrile	10	29.9	3.5×10^{-6}
	20	28.4	3.8×10^{-6}
	30	27.3	3.1×10^{-6}
Acetone	10	30	1.0×10^{-5}
	20	29	1.4×10^{-5}
	30	27	1.9×10^{-5}
Methanol	10	29.5	3.0×10^{-6}
	20	28.2	2.5×10^{-6}
	30	40	9.1×10^{-6}

It was observed that **DPA** based Zn^{2+} selective membrane electrode works well up to 20% non-aqueous content without showing any appreciable change in the slope or detection limit. However beyond this, deviations observed are considerable as shown in Figure 4c.6a. Non-aqueous tolerance limit for Ni^{2+} selective membrane goes up to 30% in case of acetonitrile, acetone and 20% in methanol case as far as slope values are considered (Fig. 4c.6b), though detection limits are slightly affected in acetone medium.

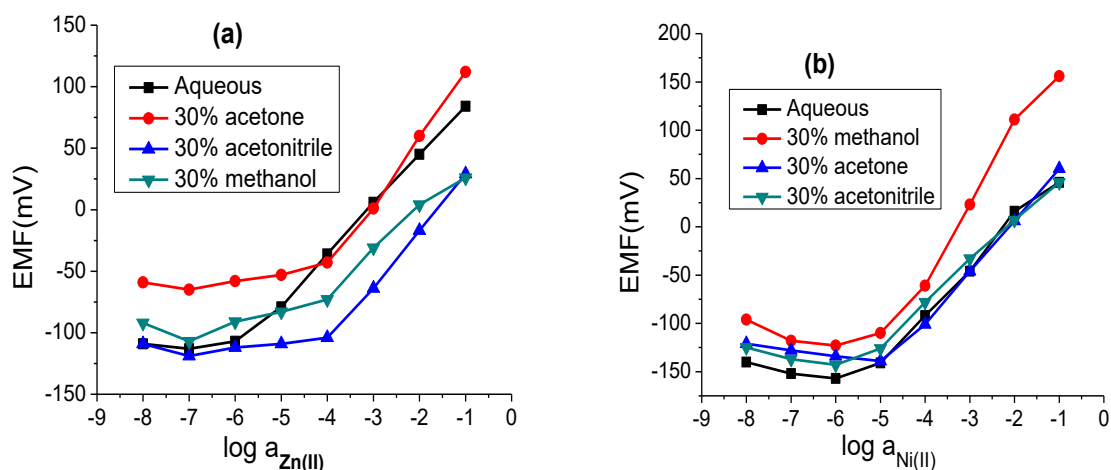


Figure 4c.6 Effect of non-aqueous medium on potential response of (a) **DPA** and (b) **TPA**

Effect of pH

The influence of the pH on the response of the zinc selective membrane electrode was examined by measuring the potentiometric responses at $10^{-2}M$ and $10^{-3}M$ concentration of zinc ions at different pH values ranging from 1 to 12. The pH was adjusted by adding small drops of HCl (0.1 M) or NaOH (0.1 M) as per requirement and results are shown in Figure 4c.7a. The emf is independent of pH in the range of 3.6 – 9.3. Ni^{2+} concentrations of $10^{-1}M$ and $10^{-2}M$ were used to monitor the pH dependence of the potential response of **TPA** based electrode. As shown in figure 4c.7b, the potentials were found to remain unaffected by the change in pH in the pH range 4.2 – 9.2. The sudden decrease of potential below 4.2 may be due to the partial protonation of the ionophore, while the increase above pH 9.2 could be due to the formation of some soluble and insoluble complexes of Ni^{2+} ions.

Effect of interfering ions on potentiometric selectivity of electrodes

Selectivity is a term which is used to describe utility of an ion selective electrode and is expressed as the potentiometric selectivity coefficient $-\log K_{M_i^{n+}B}^{Pot}$. It gives the magnitude of selectivity of an electrode towards a particular ion in the presence of other interfering ions. Potentiometric selectivity coefficients for both the electrodes were determined by IUPAC recommended fixed interference method (FIM).

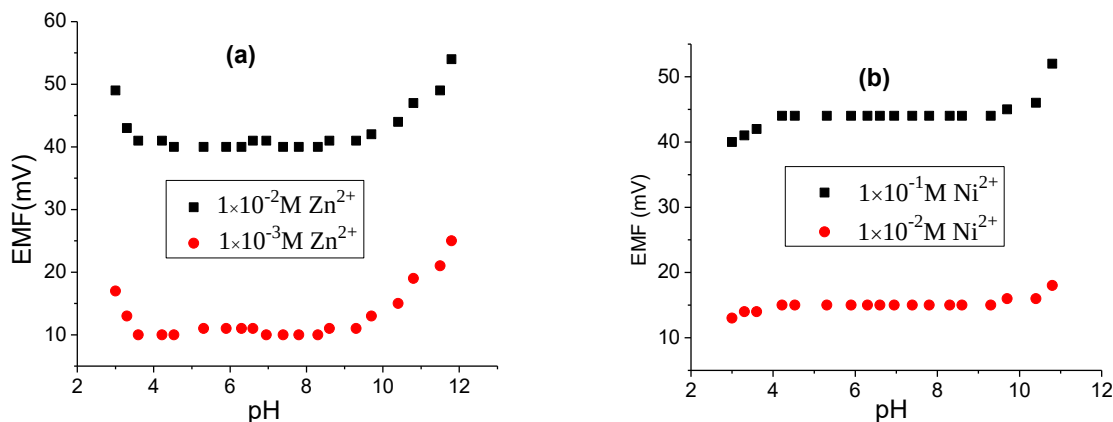


Figure 4c.7 Effect of pH on the potential response of (a) Zn (II) ISE based on **DPA** and (b) Ni (II) ISE based on **TPA**

In this method, a fixed concentration of interfering ions ($1.0 \times 10^{-2} \text{ M}$) and a varying concentration of target ion solution ranging from $1 \times 10^{-1} \text{ M}$ to $1 \times 10^{-8} \text{ M}$ was used. The potentiometric selectivity coefficients were then determined using the following expression [77]:

$$K_{AB}^{POT} = \frac{a_A}{a_B^{z_A/z_B}}$$

Where, a_A is the activity of primary ion A at the lower detection limit in the presence of interfering ion B, a_B , the activity of interfering ion B and z_A and z_B are their respective charges. The values of selectivity coefficients so determined for Zn^{2+} selective and Ni^{2+} selective electrodes are compiled in Tables 4c.7 and 4c.8, respectively. From the data, it can be concluded that there is no serious interference from common ions. The $\log K$ values of **DPA** are in the range of -2.0 to -3.1 which indicates that proposed electrode has high selectivity for Zn^{2+} over other ions and hence can be conveniently used for the determination of Zn^{2+} ions in the presence of these ions. Selectivity coefficient values in Table 4c.8 reveal that triphenylamine electrode too has reasonably good selectivity for Ni^{2+} ions in the presence of various alkali, alkaline earth and transition metal ions.

Table 4c.7 Potentiometric selectivity coefficients of Zn(II) ISE based on **DPA** by Fixed interference method

Metal ion	$\log K_{Zn^{2+}, B}$	Metal ion	$\log K_{Zn^{2+}, B}$
K⁺	-1.4	Ni²⁺	-2.0
Ca²⁺	-2.7	Cu²⁺	-2.5
Na⁺	-1.9	Sr²⁺	-2.3
Mg²⁺	-2.1	Ba²⁺	-3.1
Pb²⁺	-2.4	Cd²⁺	-1.9
Fe²⁺	-2.8	Co²⁺	-2.7

Table 4c.8 Potentiometric selectivity coefficients of Ni(II) ISE based on **TPA** by Fixed interference method

Metal ion	$\log K_{Ni^{2+}, B}$	Metal ion	$\log K_{Ni^{2+}, B}$
Na⁺	-1.0	Pb²⁺	-2.6
Sr²⁺	-3.1	Fe²⁺	-3.2
Cu²⁺	-1.9	Ca²⁺	-3.1
Cd²⁺	-2.9	Ba²⁺	-3.5
Mg²⁺	-2.8	Zn²⁺	-2.1
Co²⁺	-3.1	Mn²⁺	-3.2

Applications

The analytical applicability of the electrodes was tested by using these as indicator electrodes in the potentiometric titration of Zn²⁺ and Ni²⁺ ion solutions. Testing of **DPA** was done by titrating 25 mL of 1×10⁻² M Zn²⁺ ion solution against 1×10⁻¹ M EDTA solution. As shown in Figure 4c.8a a very good inflection point corresponding to Zn²⁺- EDTA stoichiometry was observed which shows that proposed electrode can be used for the determination of Zn²⁺ potentiometrically.

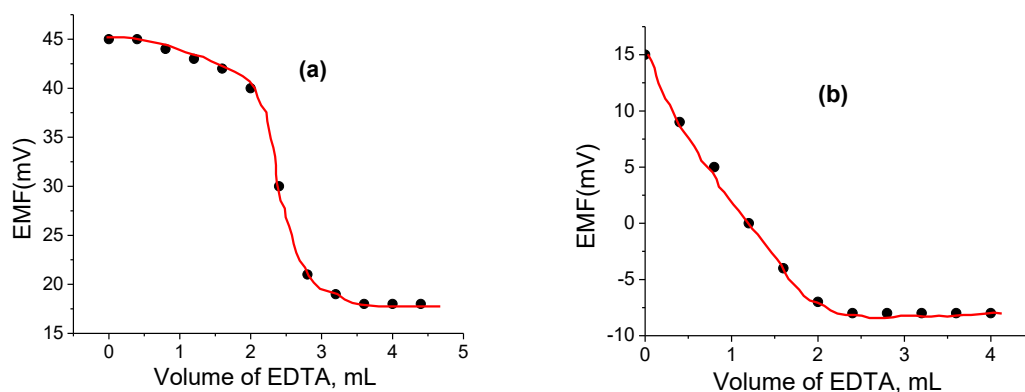


Figure 4c.8 Potentiometric titration of (a) Zn(II) (25 mL of 1×10^{-2} M) with EDTA (1×10^{-1} M) using Zn(II) selective electrode based on **DPA** and (b) Ni(II) (20 mL of 1×10^{-2} M) with EDTA (1×10^{-1} M) using Ni(II) selective electrode based on **TPA**

TPA electrode has also been applied successfully for the end point determination of Ni^{2+} in the potentiometric titration. Titration was performed by using the proposed electrode as indicator electrode for the titration of 20 mL of 1×10^{-2} M Ni^{2+} against 1×10^{-1} M solution of EDTA. The titration curve is shown in Figure 4c.8b. Curve shows sharp inflexion point corresponding to 1:1 stoichiometry of the complex. Therefore, the proposed membrane electrode can be used as indicator electrode for the determination of Ni^{2+} in potentiometric titrations.

4c.4 Theoretical studies

In an attempt to better understand the nature of ionophores and their interaction with metal ions, theoretical studies were carried out using density functional theory method. B3LYP function with 6-31G basis set was used for quantum chemical calculations of ionophores independently and along with metal ions on Gaussian 03W programme.

Quantum chemical calculations were carried out for the energy optimization of **DPA** independently and along with Mn^{2+} , Fe^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} . As shown in Table 4c.9, highest energy decrease of 1778 a.u. was observed for Zn^{2+} , thus indicating a stable complex formation of **DPA** with Zn^{2+} over other metal ions. Mn^{2+} , Fe^{2+} , Ni^{2+} and Cu^{2+} show an energy decrease of 1150, 1263, 1507 and 1639 a.u., respectively.

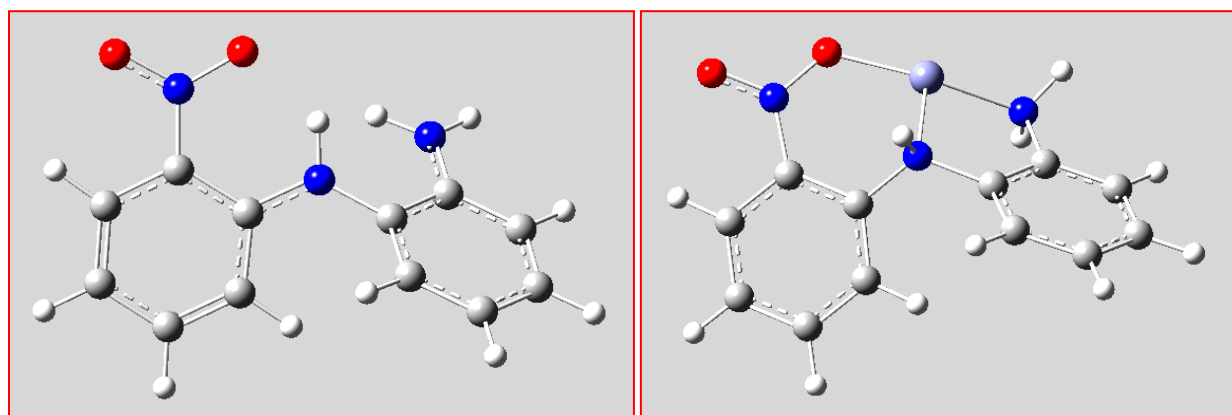


Figure 4c.9 DFT optimized structures of **DPA** and **DPA-Zn²⁺** complex. White, Red, Blue, Grey and purple spheres refer to H, O, N, C and Zn²⁺, respectively

Table 4c.9 Energy minimization study of **DPA** with some metal ions using Gaussian 03W programme

Metal ion	Energy Value (a.u.)	Energy decrease (a.u.)
DPA	-778	-----
Mn²⁺	-1928	1150
Fe²⁺	-2041	1263
Ni²⁺	-2285	1507
Cu²⁺	-2417	1639
Zn²⁺	-2556	1778

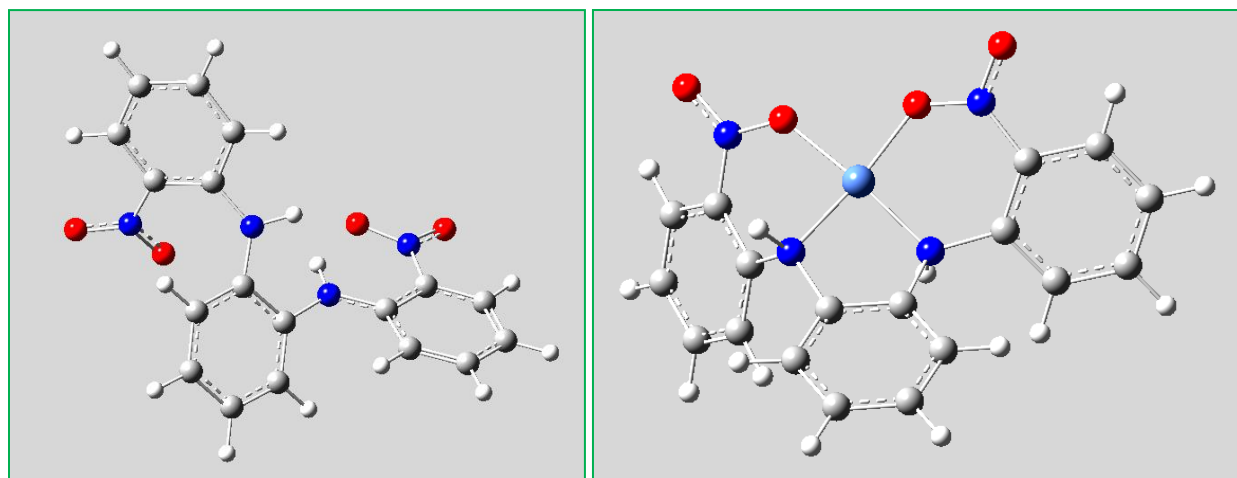


Figure 4c.10 DFT optimized structures of **TPA** and **TPA-Ni²⁺** complex. White, Red, Dark Blue, Grey and Light Blue spheres refer to H, O, N, C and Ni²⁺, respectively

Optimized geometry of ionophore reflects the presence of a pseudo cavity constituted by the three nitrogens of amino and nitro groups. In the presence of Zn²⁺, both the primary as well as secondary amine groups align themselves in a way so as to generate the best fit metal ionophore complex as shown in Figure 4c.9.

Figure 4c.10 shows the three-dimensional structure of **TPA**, in which two amine nitrogens along with one of the nitro groups are involved in composing a pseudo cavity for the trapping of metal ion. It was observed that nitro group on the other phenyl ring was pointing away, may be in order to trim down the steric crowding. However, on the addition of Ni²⁺ ions into the system, flexible nature of diphenyl amine linkage facilitates a conformational change and both the nitro groups along with two amine nitrogens start participating in complexation with Ni²⁺ ions. The values of energy optimization of uncomplexed and complexed ionophore confirm an overall increase in the stability of system after complexation. Energy decreases from – 1213 a.u. to – 2721 a.u, after addition of Ni²⁺, thus indicating the formation of highly stable **TPA – Ni²⁺** complex.

Table 4c.10 Comparison of proposed ‘DPA’ based zinc selective electrode with the reported electrodes

S. No.	Ionophore	Detection limit (M)	pH Range	Slope (mV/decade)	Ref
1	Tetraaza macrocycle [Bzo ₂ Me ₂ Ph ₂ (16)hexaeneN ₄]	2.24×10 ⁻⁶	2.5-8.5	28.5	41
2	N,N-bis (2-hydroxy -4-methoxybenzaldehyde)-2,6-di aminopyridine	7.9 ×10 ⁻⁸	4.5-10	29.5	42
3	N,N'-phenylenebis (salicylideaminato)	2.6×10 ⁻⁷	3.0-7.0	29.4	10
4	Zn-ATSC	5.0 × 10 ⁻⁸	3.5-8.0	28.5	43
5	PME- 6,7:14,15-BzO ₂ -10,11-(4-methylbenzene)-[15]-6,8,12,14-tetraene-9,12-N ₂ -1,5-O ₂	3.3×10 ⁻⁷	3.0-8.0	28.8	44
6	Dibenzo-24-crown-8	2.0×10 ⁻⁷	4.8-6.2	29.0	45
7	1,12,14-Triaza-5,8-dioxo-3(4),9(10) -dibenzoylcyclopentadeca-1,12,14-triene	1.0×10 ⁻⁸	3.5-9.2	29.2	46
8	3-[(2-Furylmethylene) amino]-2-thioxo-1,3-thiazolidin-4-one	8.5×10 ⁻⁷	3.0-7.0	29.3	47
9	N,N-Bis(acetylacetone)ethylenediamine	8.9 ×10 ⁻⁷	3.2-7.1	30.0	48
10	Bis(2-nitrophenyl)disulfide	2.0×10 ⁻⁷	2.0-9.0	29.9	49
11	Potassium hydrotris(N-tert-butyl-2-thioimidazolyl)borate	9.5×10 ⁻⁸	3.5-7.8	29.4	50
12	This work (DPA)	1.3x10 ⁻⁶	3.6-9.3	30.0	-----

Table 4c.11 Comparison of proposed ‘TPA’ based Ni(II) selective electrode with the reported electrodes

S. No.	Ionophore	Detection limit (M)	pH Range	Slope (mV/decade)	Ref
1	Tetraazaannulene macrocycle [Me ₄ Bzo ₂ TAA]	7.9×10^{-6}	2.7-7.6	30.0	39
2	<i>N,N</i> -bis-(4-dimethylamino-benzylidene)-benzene-1,2-diamine	2.0×10^{-7}	4.5-9.0	30.0	51
3	<i>N</i> -(2-hydroxybenzylidene)- <i>N</i> -(2-picolyl)ethylenediamine	3.2×10^{-6}	2.2-5.9	29.0	52
4	<i>N</i> 1, <i>N</i> 2-bis((naphthalen-1-yl)-methylene)ethane-1,2diamine	1.3×10^{-6}	3.6-7.4	29.9	53
5	2,3,7,8,12,13,17,18-octamethyl- 21H, 23H-porphine (OMP)	1.0×10^{-5}	2.0-7.0	29.0	54
6	dibenzodiazia-15-crown-4	5.6×10^{-7}	3.0-6.0	Nernstian	55
7	hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene diperchlorate	1.0×10^{-5}	1.7-5.4	Near-Nernstian	38
8	1,10-dibenzyl-1,10-diaza-18-crown-6	2.0×10^{-5}	4.0-8.0	Nernstian	56
9	5,7,8,14-tetramethyldibenzo[b,i]-1,4,8,11-tetrazacyclotetradecane	7.0×10^{-6}	2.0-7.6	29.8	57
10	This work (TPA)	2.5×10^{-6}	4.2 -9.2	30.0	-----

4c.5 References

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LIST OF PUBLICATIONS

1. **Harpreet Kaur**, Manmohan chhibber, Susheel K. Mittal* “New acyclic aryether ionophores as potentiometric sensors for Ca(II) and Fe(II) ions.” *MAPAN-Journal of Metrology Society of India* (In press) (IF: 1.0)
2. **Harpreet Kaur**, Manmohan chhibber, Susheel K. Mittal* “Acyclic arylamine based ionophores as potentiometric sensors for Zn(II) and Ni(II) ions” *C Journal of Carbon Research* (under Review).
3. **Harpreet Kaur**, Manmohan chhibber*, Susheel K. Mittal “New triphenylethers for the spectrochemical sensing of calcium ions.” *Indian Journal of Chemistry-B* (under Review).

Papers/ Posters in Conferences

1. Poster presentation in National conference on “New Frontiers in Chemical Sciences” (NFCS-01) held on Nov. 15, 2014 at Khalsa College, Patiala.
2. Poster presentation in International conference on “Recent Trends in Engineering and Material Sciences”(ICEMS- 2016) held on March 17-19, 2016 at JNU, Jaipur.
3. Oral presentation in International conference on “Ecosensitive Developments in Science and Technology” (ESDST) held on January 20-21, 2017 at BBSBEC, Fatehgarh Sahib.