SYNTHESIS AND CHARACTERIZATION OF PROTIC AMMONIUM BASED IONIC LIQUIDS

M. Sc THESIS

A

DISSERTATION SUBMITTED FOR THE PARTIAL

FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF

MASTER OF SCIENCE (M. Sc)

IN

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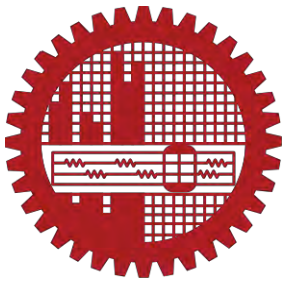

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My Beloved Parents
&
Honorable Supervisor

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THESIS ACCEPTANCE LETTER

The thesis titled **"Synthesis and Characterization of Protic Ammonium Based Ionic Liquids"** Submitted by **KHADIZA,** Roll No: 0416032602F, Registration No: 0416032602, Session: April'2016 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Master of Science (M.Sc) in Organic Chemistry on **14 May, 2019.**

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I hereby certify that this material, which I now submit for assessment on the program of study leading to the award of M.Sc is entirely my own work, and I also declare this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma.

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ABSTRACT

Ionic Liquids (ILs) have attracted extensive research interest in recent years as environmentally benign solvents and it has also been considered as the "engineering solvents" having its tunable physical and chemical properties. ILs are typically consist of organic nitrogen-containing heterocyclic/aliphatic cations and inorganic or organic anions. The ILs designed and synthesized for carrying out specified task are referred as functionalized ILs, which show great application potential in various processes. The efforts to produce functionalized ILs, characterized them, and evaluate their properties and applications are presented in this thesis.

A series of Seven (**7**) achiral and chiral protic diisopropylethylammonium based ILs were designed, synthesized and characterized. Out of these six are achiral, one is chiral based ILs. All diisopropylethylammonium based ILs were characterized by analytical data obtained from: FT-IR, UV-VIS, ^{1}H-NMR spectroscopy.

Anti-microbial and toxicity studies were carried out using the well-diffusion technique with ILs solutions of two different concentrations. The six human pathogens were as follows: *Bacillus cereus (+), Staphylococcus aureus (+), Sarcina lutea (+), Eschericia coli (-), Salmonella typhi (-), Pseudomonas aeruginosa (-).*

Two protic Diisopropylethylammonium based ILs were chosen to employ in Mannich reaction to synthesis of β-amino carbonyl compounds and esterification reaction. The synthesized protic ionic liquids (PILs) showed catalytic effect on Mannich reaction and esterification reaction in very short time.

Keywords: Ionic liquids, Engineering solvent, Mannich reaction, β-amino carbonyl compound, Esterification reaction, Diisopropylethylammonium cation.

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Author

(Khadiza)

Compounds List in this Thesis

Code No.	Compound name	Abbreviation	No.
K-IL01	*N,N*-Diisopropylethylammonium formate	[DIPEAH][F]	**1**
K-IL02	*N,N*-Diisopropylethylammonium acetate	[DIPEAH][A]	**2**
K-IL03	*N,N*-Diisopropylethylammonium propionate	[DIPEAH][P]	**3**
K-IL04	*N,N*-Diisopropylethylammonium butyrate	[DIPEAH][B]	**4**
K-IL05	*N,N*-Diisopropylethylammonium trifluoroacetate	[DIPEAH][TFA]	**5**
K-IL06	*N,N*-Diisopropylethylammonium 2-bromopropionate	[DIPEAH][2BrP]	**6**
K-IL07	*N,N*-Diisopropylethylammonium 2-chloroacetate	[DMAPyH][2ClA]	**7**

CONTENT

CHAPTER 4

CATALYTIC EFFECT OF SYNTHESIZED IL8

MANNICH REACTION

ESTERIFICATION REACTION

ABBREVIATION

Full name /Elaborations	Abbreviations
Acetic acid	AA
Achiral ionic liquid	AIL
2-Chloro acetic acid	CAA
1-Butyl-3-methylimidazolium	BMIM
1-Benzylpyridinium chloride	BPC
Chiral ionic liquid	CIL
1,4-Diazabicyclo [2.2.2] octane	DABCO
Dimethyl formamide	DMF
Dimethyl sulfoxide	DMSO
Octyl formate	OA
Formic acid	FA
Highest occupied molecular orbital	HOMO
Lowest unoccupied molecular orbital	LUMO
Ionic liquids	ILs
Minimum inhibitory concentration (MIC)	MIC
Mannich Reaction	MR
Multi-component Reactions	MCRs
Nuclear magnetic resonance	NMR
Protic ionic liquid	PIL
Potato dextrose agar	PDA
Room temperature ionic liquid	RTIL
Thermo-gravimetric analysis	TGA
Tetrahydro furan	THF
Thin layer chromatography	TLC
Task specific ionic liquid	TSIL
Volatile organic compound	VOC
N,N-Diisopropylethylammonium trifluoroacetate	[DIPEAH][TFA]

Chapter 1

Introduction Of Ionic Liquids

CHAPTER 1

What is an Ionic Liquid?

An ionic liquid (IL) is a liquid containing ions i.e. organic cations and anions. Although in some papers, ionic liquids are referred as 'molten salts', there is an arbitrary distinction between molten salts and ionic liquids [1,2]. Ionic liquids are defined as pure compounds, consisting of cations (mostly organic moiety) and anions, which melts at or below 100 °C [2,3] whereas, salts which have high melting points, are highly viscous and corrosive are termed as 'molten salts' (liquid NaCl at 803 °C). In some cases, ILs are liquid at room temperature, hence can be called 'room temperature ionic liquids' (RTILs).

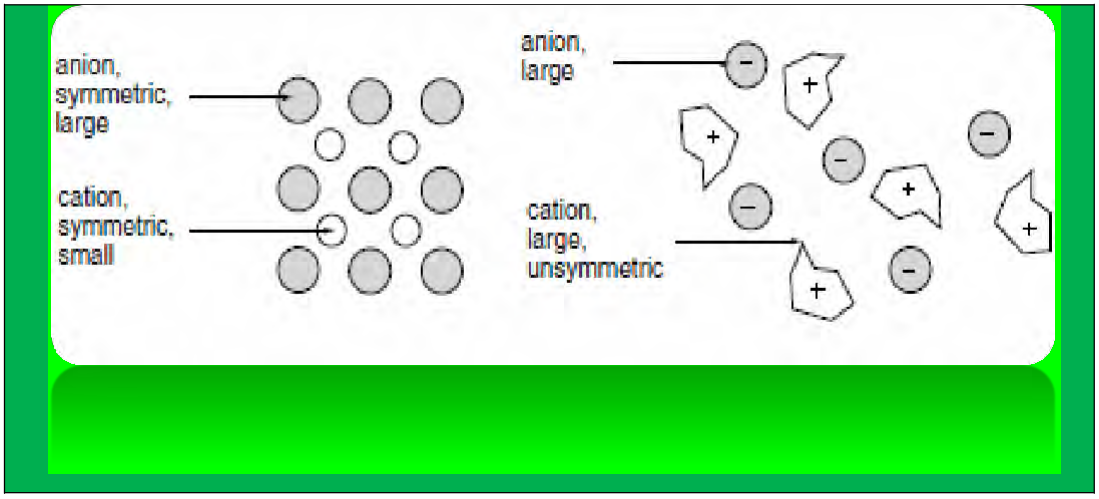


Figure 1.1: Comparison of cationic symmetry in NaCl (left) and ionic liquids (right).

The most characteristic feature, and which may be the reason why ionic liquids have low melting points, is that usually they are composed of a bulky organic cation with a low degree of symmetry and bulky inorganic/organic anion as shown in Fig. 1.6 [4]. The huge interest in such compounds is based on the fact that they possess several attractive properties in particular negligible vapor pressure, high chemical and thermal stability, non-flammability, high ionic conductivity, wide electrochemical potential window and particularly their ability to act as catalysts [2,5] In addition, many of their physico-chemical properties can be changed substantially by variation of the cation and the anion; thus, they are „tunable“ to desired reaction. For this reason, ILs have been referred to as “designer solvents”“ in several publications.

Brief History of Ionic Liquids:

Although they have been of particular interest in the last 15 years, they have been known to exist for almost a century. The first ionic liquid was reported in 1914 by P. Walden, [6] when ethylamine was reacted with concentrated nitric acid to form $[EtNH_3][NO_3]$. The first application based synthesis of ILs was performed by Hurley and Weir [7] in 1948 where the final IL was synthesized from 1-ethylpyridinium chloride and aluminiumchloride. This chloroaluminate IL was applied in the electrode position of aluminium, later on two other groups (Gale and Nardi) discovered that 1-butylpyridinium chloride-$AlCl_3$ gave better results. [8] This class of ILs, with $[AlCl_4]$- as the anion, is called 'first generation ILs'. In 1967, Swain *et al*. [9], reported use of tetra-*n*-hexylammonium benzoate, as a solvent for their kinetic and electrochemical studies.

In late 70s, Dr. L. A. King, J. Wilkes and R. Carlin were working under a US Air Force Academy project aimed at finding a replacement for LiCl-KCl eutectic mixtures. As the melting temperature for LiCl-KCl mixture is 355 °C, this causes problems with the materials inside the battery, as well as incompatibilities with any nearby devices [10]. With extensive research, they found that NaCl-$AlCl_3$ (which was remarkably close to be an IL by definition) has a eutectic composition possessing melting point of 107 °C, and works well in batteries. The physico-chemical properties and electrochemical behavior was determined for this class of salts to file a patent. In extensive research, Wilkes and Hussey were working on alkylpyridinium chloroaluminate salts with reference to Hurley and Weir's work [7a] reported in 1948, and found that the alkylpyridinium cation suffers from being easy to reduce chemically and electrochemically. They moved their attention on to 1-ethyl-3-methylimidazolium, (as it is resistant towards reduction) and prepared various compositions of [emim]Cl-$AlCl_3$ and discovered exceptionally well behaved new electrolyte for batteries [11]. As the anion contains Lewis acid, these ILs were applied as catalysts in Friedel-Craft reactions [12] and as solvent in Polymerization [13,14].

Although ILs gave excellent results, their biggest disadvantage was their reactivity towards water. Hence efforts were taken to prepare water stable ILs, leading ultimately to Mike Zaworotko *et al*. [15] synthesizing a new series of [emim] based ILs, with iodide, tetrafluoroborate, hexafluorophosphate, nitrate, sulphate and acetate anions. These air and water stable ILs were referred to as 'second generation ILs'. Unlike the alkyl imidazolium chloroaluminate ILs, second generation ILs could be synthesized out of a glove box. These ionic liquids are largely water tolerant, however, prolonged exposure to moisture can cause

some changes in their physical and chemical properties. It was found that the undried ionic liquid [bmim][PF_6] attacks gold substrate and its aggressiveness increases with the increase in water content. This is due to the formation of HF as a result of decomposition of the ionic liquid in the presence of water. Therefore, ionic liquids based on more hydrophobic anions such as tri-fluoro methane sulfonate ($CF_3SO_3^-$), *bis* (trifluoro methane sulfonyl)imide [$(CF_3SO_2)_2N^-$] and *tris*-(trifluoro methane sulfonyl)methide [$(CF_3SO_2)_3C^-$] have been developed [16-18].

Types of Ionic Liquids

A simple IL consists of one cation and one anion. The anions are generally small and the cations bulky with alkyl chains. Some usually used anions for simple ionic liquid systems are Cl, Br, BF_4, CF_3SO_3, OTf, $N(SO_2CF_3)_2$, NTf_2 etc. There are a few dissimilar commonly used cations for ILs, the commonly studied ones are the 1-alkyl-3-methyl-imidazolium cations. Other cations are phosphorus or nitrogen containing organic ions with attached alkyl chains of varied length. The name of an ionic liquid first states the cation followed by the anion. For the most commonly studied systems (Imidazolium based cations) the cations are named according to the alkyl chains lengths followed by Imidazoliums [19]. A 1-butyl-3-methyl-imidazolium cation is sometimes abbreviated as C_4C_1Im, BMIm, BMIM, bmim or BuMeIm. The anions are generally named in accordance to general principles, e.g. Ac is meaning Acetate. More than 600 ILs systems can, in principle, be generated from around 10 simple anions such as BF_4- and PF_6^- and the1-alkyl-3-methylimidazolium cation substituted with various alkyl groups in the 2-, 4-, or 5-position, or N-alkylpridinium substituted in the 3- or 4-position. When hetero-polyanions and tetralkylammonium and tetraalkyl-phosphonium cations are added to the list, a grand total of more than a quarter of a million IL systems is possible. With this enormous variety, it is usually feasible to tailor the solvents to specific chemical reactions. ILs has a range of physical-chemical properties that can be tuned with an accuracy that is hard to see for a given reaction. According to their properties and uses they are classified into following types: 1st generation ILs; 2nd generation ILs; 3rd generation ILs.

First Generation ILs

The first IL known was ethylammonium nitrate, reported in 1914 by Walden but attracted little interest. The first generation of ILs with widespread utilization was mainly composed of cations like dialkylimidazolium and alkylpyridinium derivatives, and anions like

chloroaluminate and other metal halides which have been described as toxic and non-biodegradable [20]. The most common anions are chloroaluminate or other metal halide anions that react with water and thus are not suitable for biotransformations. This generation of ILs was also oxygen-sensitive [21] and can only be handled under inert-gas atmosphere due to the hygroscopic nature of $AlCl_3$.

In the 1980s, Wilkes *et al.* started the extensive research on first generation ILs. However, due to these limitations, the progress in their use was limited. For this reason, research was directed towards the synthesis of air- and water-stable ILs, the second generation of ILs [21].

Second generation ILs

After one decade the second generation of ILs appeared. The water- and oxygen reactive anions were replaced by halides (Cl^-, Br^-, I^-) or anions such as BF_4^-, PF_6^- and $C_6H_5CO_2$, which are stable to water and air. Cations such as dialkylimidazolium or alkylpyridinium were maintained, and ammonium and phosphonium were added [21]. These ILs present interesting properties such as lower melting points, different solubility"s, viscosities, etc in classic are organic solvents [22]. Due to these properties, the second generation attracted a great interest in various fields, and research in ILs experienced an important boost from the 1990"s. The first reports of bio-catalysis with ILs were published in the beginning of 2000´s [23]. One of the disadvantages of these ILs is the high cost. According to [24], the high costs are related to starting materials (namely fluorinated components) and purification of final product required in the preparation. The most important disadvantage of the second generation is the toxicity, which in general is similar to those of chlorinated and aromatic solvents [25]. However, this second generation of ILs attracted the attention of the wide scientific community and has been providing interesting and novel applications in different areas. This generation of ILs is the most studied and a great number of applications in bio-catalysis have been published. The activity, stability, kinetic and thermal stability of different enzymes such as oxidases, lipases or cellulases has been studied, and synthesis of various products has been carried out [26].

Third generation ILs

The third generation of ILs (advanced ILs) is based on more hydrophobic and stable anions such as $[(CF_3SO_2)_2N^-]$, sugars, amino or organic acids, alkylsulfates, or alkylphosphates and cations such as choline. The cations and/or anions used are biodegradable, readily available,

and present lower toxicities. Besides, a new class of solvent systems, called deep eutectic solvents (DES), is more hydrophilic than the second generation, and in general is water-miscible. DES are mixtures of salts (in general they are not liquids at room temperature) such as choline chloride, and uncharged hydrogen bond donors such as amines, amides, alcohols, carboxylic acids, urea, or glycerol [27]. A typical example is the choline chloride/urea mixture, which produces a DES with a melting point of 12 °C, at concentrations around 50%). The advantages of the third generation are: lower costs (similar to organic solvents), simple to prepare, biodegradable, do not require purification, the purity of the starting materials determines the final purity and uses anions and cations with low toxicity. As this generation is recent, few works have been published [28]. The transetherification of ethyl valerate with 1-butanol, showed good activity in DES, and in choline chloride: glycine the activity was similar to activity in toluene for all lipases. The third generation will reach the commercial level soon in market. On the based proton, ILs can be divided into two broad categories: a. Protic ILs (PILs): PILs are produced through proton transfer from a Bronsted acid to a Bronsted base; b. Aprotic ILs (APILs): APILs are produced which cannot transfer proton from a Bronsted acid to a Bronsted base. According to the cation segments, ILs are usually categorized into four types: alkylammonium, dialkylimidazolium, phosphonium and N-alkylpyridinium based ILs.

Quaternary Ammonium based ILs:

Ammonium cations, also known as quats, are positively charged polyatomic ions of the structure NR_4^+, R being an alkyl group or an aryl group [29]. The alkyl or aryl groups are directly connected with the nitrogen atom to form a positively charged central as cation. Unlike the ammonium ion (NH_4^+) and the primary, secondary, or tertiary ammonium cations, the quaternary ammonium cations are permanently charged, possess independent pH in their solutions [30]. Quaternary ammonium salts (quats) are quite well known and have widespread industrial utilization as surfactant agents due to their surface activity [31] and other useful properties [32]. In 1890, Menschutkin synthesized quats by the nucleophilic substitution reaction of tertiary amines with an alkyl halide, and the „Menschutkin reaction" is still regarded as the best method for the preparation of quat salts [33]. Quats are generally known to be bioactive and have high anti-microbial activity [34], as has been shown for water-soluble compounds that contain alkyl chains of length C_8 to C_{16} [35]. The Quaternary Ammonium based ILs (Figure 1.1) consists of ammonium based cations with different types of anions

such as carboxylate, nitrate, sulphate, chloride, fluoride, phosphate etc, where, R_1, R_2, R_3 and R_4 = H or different alkyl or functionalized alkyl or aryl moiety.

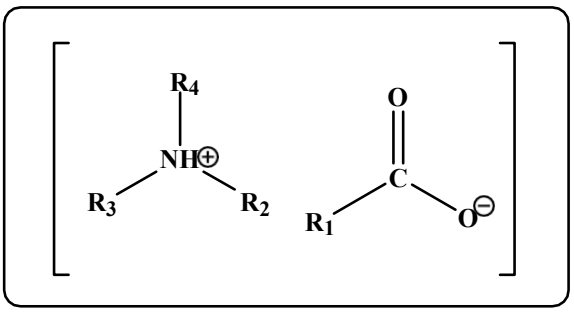


Figure 1.2: Quaternary ammonium carboxylate ILs.

ILs, in general, differs from the classical ammonium salts, at least in one very important aspect in the field of solution Chemistry. ILs possess pre-organized structures, mainly through hydrogen bonds [36-38], which induce 3D structure dimensionality in these systems (IL effect). Conversely, aggregates of classical salts display charge-ordered structures. Since ILs can form extended hydrogen-bond networks at the liquid state, therefore they demonstrate this very unique property of high self-organization on the nano-molecular scale, and can be classified as supramolecular fluids [39]. This nano-scale structural organization of ILs can be used to drive the spontaneous extended ordering of nanomaterials [40-41]. Some of the classical examples that Ionic Liquids as Designer Solvents for the Synthesis of Metal Nano-particles have illustrated this concept include IL-mediated synthesis of ordered mesoporous materials [41] and microporous aluminophosphates, where in ILs served both as the solvent and structure-directing agents [29,42]. ILs are environmentally friendly solvents. They can replace volatile organic compounds because they have almost no vapor pressure [43]. They have demonstrated their potential ability, and they are also a unique design of solvents. The properties of ILs can be adjusted by the cation/anion structure to satisfy specific application requirements.

Properties of Ionic Liquids:

ILs possess several properties over conventional organic solvents, which make them environmentally compatible, such as:

- ILs has the ability to dissolve many different organic, inorganic and organometallic materials.
- ILs is highly polar.

- ILs consists of loosely coordinating bulky ions.
- ILs does not evaporate since they have very low vapor pressures.
- ILs is thermally stable, approximately up to 300 °C.
- Most of ILs has a liquid window of up to 200 °C which enables wide kinetic control.
- ILs has high thermal conductivity and a large electrochemical window.
- ILs is immiscible with many organic solvents.
- ILs is non-aqueous polar alternatives for phase transfer processes.
- The solvent properties of ILs can be tuned for a specific application by varying the anion-cation combinations.

Ionic liquids are considered as green solvents and often are used as catalysts as well. Hence the determination of physical and chemical properties becomes extremely beneficial if ILs have to be incorporated in industrial applications. In order to encourage a widespread use of ILs, they should be cheaper to synthesize, recyclable, and robust to endure all types of processing conditions. Physical properties such as melting point, boiling point, solubility, refractive index, density, and viscosity, are related to the mechanics and engineering aspects associated with the process. For example, density, viscosity, and surface tension will determine critical parameters including rates of liquid–liquid phase separation, mass transfer and power requirements for stirring and mixing. Properties such as the structuredness, normalized polarity (EN), polarizability (π^*), hydrogen bond donor acidity (α), and hydrogen bond acceptor basicity (β) are more obviously related to the solubilities, partition coefficients, and reaction kinetics [44,45].

The physical and chemical properties of ionic liquids can be specifically varied over a wide range by the selection of suitable cations and anions. Toxicity and biodegradation are the properties which give information about ILs, such as their biological behavior and environmental impact. Knowledge of physico-chemical and biological properties enables chemists, to choose specific IL for a chemical process.

Melting Point:

By definition, the melting point is an evaluative property of ILs. The point of significance is the relationship between structural & chemical composition of an IL and melting point. The main reasons for ILs having low melting points, despite being a salt, are the low symmetry of the cation, [46] weak inter-molecular interactions, and a diffuse distribution of charge in

cation and/or anion [47]. Table 1.1 [48, 49] illustrates the effect of the cation clearly; high melting points are characteristics for alkali metal chlorides, whereas chlorides with organic cations melts at <100 °C .

Table 1.1: Melting points of various chlorides.

Salt	Melting point(°C)
NaCl	803
KCl	772
[dmim][Cl]	125
[emim][Cl]	87
[bmim][Cl]	65

Comparison of melting points of different salts of [emim] emphasises that, in most cases, the increasing size of an anion with the same charge leads to a further decrease in the melting point (Table 1.2) [50,51]. Along with an anion choice, variation in the alkyl chain length in the cation can achieve fine-tuning of the melting point.

Table 1.2: Influence of anions on melting point of ILs.

Imidazolium salts	Melting points (°C)
[emim][Cl]	87
[emim][NO_2]	55
[emim][NO_3]	38
[emim][$AlCl_4$]	7
[emim][BF_4]	6[a]
[emim][PF_6]	62
[emim][CF_3SO_3]	- 9
[emim][CF_3SO_2]	-14
[emim][NTf_2]	- 3
[a] glass transition.	

Vapor pressure and Thermal stability:

Ionic liquids have no measurable vapor pressure which is a significant advantage, since separation of a reaction mixture becomes more effective as a method of product isolation. The well-known problem of azeotrope formation between the solvent and the products does not arise. Thermal stability of ionic liquids depends on the strength of carbon-heteroatom and hetero atom-hydrogen bond. For example, ionic liquids synthesized by the protonation of an amine or phosphine have low thermal stability.

Most of the ionic liquids are shown to be stable up to 400 °C, except some trialkylammonium salts which decompose at 80 °C in vacuo depending on the boiling point of the corresponding amine [52,53]. Recent reports have described the TGA of imidazolium salts and noted that the thermal decomposition is heavily dependent on the salt structure [54]. These reports also indicate that experiments performed under N_2 or air produce the same results.

Table 1.3: Thermal decomposition temperature for ILs.

Ionic Liquid	**Decomposition Temperature** (°C)
[emim][Cl]	285
[pmim][Cl]	282
[emim][Cl]	254
[hmim][Cl]	253
[omim][Cl]	243
[bmim][I]	265
[bmim][BF_4]	403
[bmim][PF_6]	349
[bmim][NTf_2]	439

The onset of thermal decomposition is furthermore similar for the different alkyl chain lengths on imidazolium but appears to decrease as the anion hydrophilicity increases (Table 1.3). The general trend for the thermal stability has been [PF_6^-] > [NTf_2^-] ~ [BF_4^-] > halides.

Viscosity:

One of the barriers in the application of ILs arises from their high viscosity. High viscosity may reduce the rate of organic reactions via reduction in the diffusion rate of the reacting species. Current research for new and more versatile ILs is driven, in part, by the need for materials with low viscosity. The viscosity of ionic liquids is essentially determined by their tendency to form hydrogen bonding and the strength of their Van der Waals interactions [55]. It is normally higher than that of water, ranging between 10-200 mPa.S, similar to those of vegetable and medium crude oils, and decreases with increasing temperature [56]. Increasing the alkyl chain length or fluorination of the cation leads to an increase in viscosity [57]. This is due to stronger van der Waals forces between cations leading to an increase in the energy required for molecular motion. For example, an increase in viscosity was observed for the 1-butylmethylimidazolium IL when the [$CF_3SO_3^-$] anion was replaced with the [n-$C_4F_9SO_3^-$] ion and from the [CF_3COO^-] ion to the [n-$C_3F_7COO^-$] ions.

Table 1.4: Influence of alkyl chain in cation and fluorinated anions on viscosity of ILs at 25 °C.

Ionic Liquid	**Viscosity** (mPa.s)
[emim][Cl]	43
[bmim][BF_4]	233
[hmim][BF_4]^a	314
[bmim][CF_3SO_3]	90
[bmim][*n*-$C_4H_9SO_3$]	373
[bmim][CF_3CO_2]	73
[bmim][*n*-$C_3F_7CO_2$]	182
[bmim][PF_6]	450
[bmim][NTf_2]	52

[a]measured at 20 °C

The ability of anions to form hydrogen bonds has a pronounced effect on viscosity. Fluorinated anions such as [BF_4^-] and [PF_6^-] form viscous ionic liquids due to hydrogen bonding. Table 1.4 [58] shows the variation in viscosity with alkyl chain length and anion. The strength of hydrogen bonding decreases in the order [PF_6^-] > [BF_4^-] > [NTf_2^-] which results in a decrease of viscosity.

Density:

The density of ILs is a property which affects the phase separation in biphasic media, diffusion coefficients and mass transfer of reactants when they are used as a reaction media. In general, they are denser than water with values ranging from 1 to 1.6 g/mL.

Table 1.5: Densities of different imidazolium ILs at 25 °C.

Ionic Liquid	**Density** (g/mL)
[bmim][Cl]	1.08
[hmim][Cl]	1.03
[omim][Cl]	1.00
[bmim][I]	1.44
[bmim][BF_4]	1.12
[bmim][PF_6]	1.36
[bmim][NTf_2]	1.43
[bmim][CF_3CO_2]	1.21
[bmim][CF_3SO_3]	1.29

Density of an ionic liquid depends on the length and type of substituent in the cation, and also on the kind of anion (Table 1.5). The molar mass of the anion, [54] alkyl chain length and bulkiness of the cation significantly affects the overall density of ILs. Density is also temperature dependent, as the temperature rises from 293 to 313K, the density of [emim][BF_4] decreases linearly [44].

Solvation ability and polarity:

The solvation ability of an IL determines the molecular dynamics of reactants and hence affects the rate of reaction. It is a well-known fact that IL solubilizes both polar and non-polar solutes depending on the substituents on the cation and anion. The more lipophilic substituents on the cation, the more it dissolves non-polar solutes. e.g. 1-octene was found to be 2500 times more soluble in methyl-tri-*n*-octylammonium tosylate than in methyl-tri-*n*ethylammonium tosylate [59]. The influence of the anion on solvation characteristics of ILs can be demonstrated in an impressive fashion by the examples of water solubility of different salts of [bmim]. While [bmim][Br], [bmim][CF_3COO], and [bmim][CF_3SO_3] are highly water soluble, [bmim][PF_6] and [bmim][NTf_2] form biphasic mixtures. The water content of [bmim][NTf_2] after mixing and separating with water is only 1.4 w/w % at 20 °C [58].

During solvation by ILs, translational polarization plays a key role (whereas in molecular solvents orientational polarization occurs). Anions arrange themselves close to the positive head of solute and vice versa (Fig. 1.3) [60].

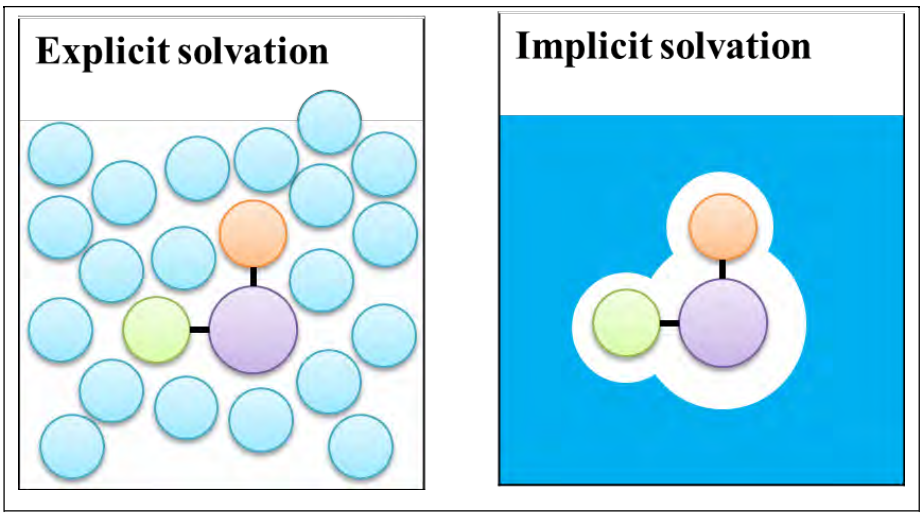


Figure 1.3: Solvation through translational polarization.

As a consequence, the composition of ILs varies depending on the spatial position around the solute or, in other words, becomes inhomogeneous.

Now, polarization of the solvent is dependent on solvent polarity, which is usually determined in a purely empirical fashion. Empirical solvent polarity parameters are derived from the measured absorption maxima of solvatochromic and fluorescent dyes (Fig. 1.4), which reflects the solvating ability of a solvent comprehensively [61].

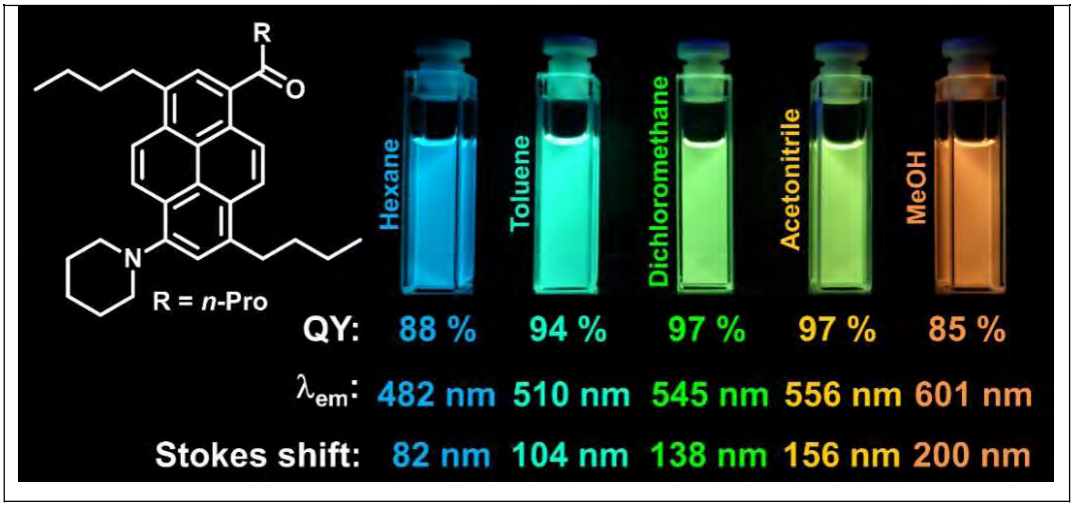


Figure 1.4: Solvatochromic and fluorescent dyes.

For the evaluation of polarity parameters, partition coefficients and sometimes reaction rates are considered as an exact determination would not be possible using solvatochromatic dyes alone. Probably the most widely used empirical scale of polarity is the $E_{T(30)}$ scale.

$$E_{T(30)}\,(\text{in kcal mol-1}) = 28592/\lambda_{max}$$

Where λ_{max} (in nm) is the maximum absorbance by zwitterionic Reichardt‟s dye. Often a normalized scale of $E_{T(30)}$ polarity, E_N^T is used which is obtained by assigning water the value of 1.0 and tetramethylsilane zero. The solvatochromic shift of this probe is strongly affected by the hydrogen- bond donor ability of the IL, due to it is structure which stabilizes the ground state more than the excited state (Fig. 1.4). The $E_{T(30)}$ scale is therefore, largely but not exclusively, a measure of hydrogen-bonding acidity of the solvent system. The E_N^T values of several ILs are reported in Table 1.6 [62].

Table 1.6: E_N^T values for solvents

Solvents	E_N^T
Water	1.00
Methanol	0.762
Dichloromethane	0.309
Toluene	0.100
Acetone	0.350
[bmim][BF_4]	0.670
[bmim][PF_6]	0.669
[bmim][OTf]	0.656
[bmim][NTf_2]	0.644
[bmim][SbF_6]	0.673
[bm_2im][BF_4]	0.576
[bm_2im][NTf_2]	0.541

The alkyl chain length for the 1-alkyl-3-methylimidazolium ILs hardly affects E_N^T values which are similar to that for ethanol (E_N^T = 0:65), but the introduction of a methyl at C-2- reduces the solvent polarity [62b].

Refractive index:

The refractive index of a medium is the ratio of the speed of light in a vacuum to its speed in the medium. It is also the square root of the relative permittivity of the medium at that frequency. This parameter is related to polarizability /dipolarity (π*) of the medium and the excess molar refraction. The values found for [bmim] salts are comparable to those for organic solvents.

Table 1.7: Refractive index [54]

Ionic liquid	Refractive index
[bmim][PF_6]	1.409
[bmim][I]	1.572
[bmim][NTf_2]	1.427
[hmim][Cl]	1.515
[omim][Cl]	1.505
[omim][PF_6]	1.423

Reported data suggests that increasing length and branching of alkyl chain on the cations increases the refractive index (Table 1.7). Changing the anion of the IL also affects the refractive index with less polarizable anions giving lower values [63].

Surface tension:

Surface tension may be a key property in multiphase processes. ILs are widely employed in transition metal catalyzed reactions carried out under multiphase conditions. Especially, the extraction of products occurs at the interface between the IL and the overlying organic phase. These reactions should therefore be dependent on the access of the catalyst to the surface and the transfer of the products across the interface i.e. the rates of these processes depend on surface tension. In general, liquid/air surface tension values for ILs are somewhat higher than those for conventional solvents [(3.3-5.7) $\times 10^{-4}$ N.cm^{1}], although not as high as for water.

Table 1.8: Surface tension for imidazolium ILs.

Ionic liquids	**Surface tension** (dyne/cm)
Water	71.9
[bmim][I]	54.7
[bmim][BF_4]	46.6
[bmim][PF_6]	48.8
[bmim][NTf_2]	37.5
[hmim][Cl]	42.5
[hbim][PF_6]	43.4
[omim][Cl]	33.8
[omim][PF_6]	36.5

Surface tension values vary with temperature and are affected by the alkyl chain length, decreasing with increasing chain length (Table 1.8) [54]. For a fixed cation, ILs with a bulky anion have higher surface tension [64].

Toxicity & biodegradation:

Volatile organic compounds (VOCs) in current industrial applications are causing concerns due to their toxicity, both towards process operators and the environment [65]. ILs being termed as 'green solvents', due to their properties, are considered as alternatives to traditional solvents. Despite the 'green' aspects of ILs, it is irresponsible to ignore the ultimate fate of ILs when released into the environment. Hence the evaluation of the toxicity of ILs becomes inevitable.

Biodegradation can be defined as a process “by which microbial organisms transform or alter (through metabolic or enzymatic action) the chemicals introduced into the environment” [66].

There are two main types of biodegradation i.e. aerobic biodegradation and anaerobic biodegradation. Aerobic biodegradation takes place in the presence of oxygen, whereas anaerobic biodegradation occurs in the lower stratum of soil or sediments, which lack molecular oxygen. Heterotrophic microorganisms utilize organic compounds as both carbon and energy sources for growth. The organic chemicals are transformed mainly by enzymes such as esterases, oxidases, etherases and sulphatases present in microorganisms.

In the early 90‟s, Boethling and co-workers [67,68] studied the structure-biodegradability relationship and suggested a number of factors that can increase the biodegradability of an organic compound, which are as follows;

(i) Presence of phenyl rings, and unsubstituted linear alkyl chains (>4 carbons in chain length), (ii) groups that provide possible sites for enzymatic hydrolysis (especially oxygen atoms in the form of hydroxyls, aldehydes, or carboxylic acids).

Furthermore, the authors also suggested that the presence of some functional groups will cause greater resistance of a compound to biodegradation, for instance halogens, nitro, nitroso, branched alkyl chains and fused ring systems all can result in decreased biodegradability. These observations enabled researchers to work towards the rational design and synthesis of biodegradable organic compounds.

Biodegradation studies are carried out to evaluate the environmental fate of the organic compounds. Due to the variety of biodegradation mechanisms in the natural environment, a number of methods are applied to test biodegradation of chemicals. The methods in common use are the Sturm test, closed bottle test [approved by The Organization for Economic Cooperation and Development (OECD 301B and D respectively)] and the BOD_5 test. As mentioned earlier in this chapter, the determination of toxicity and biodegradation of ionic liquids allows researchers to evaluate the 'greenness' of ILs, which consequently enables them to choose greener ILs for further applications. Several scientists around the globe, for instance, P. Scammells, N. Gathergood, S. Stolte etc, are already working in this area. Details on toxicities and biodegradation are discussed in a separate chapter.

Some more properties of ionic liquids are also studied in detail, in particular, conductivity, electrochemical properties, [69] acidity and coordination ability [70]. All of these properties have persuaded chemists to utilize ILs in different fields of chemistry. Seddon and Plechkova put forward a pictorial representation for applications of ILs (Fig. 1.5) [71].

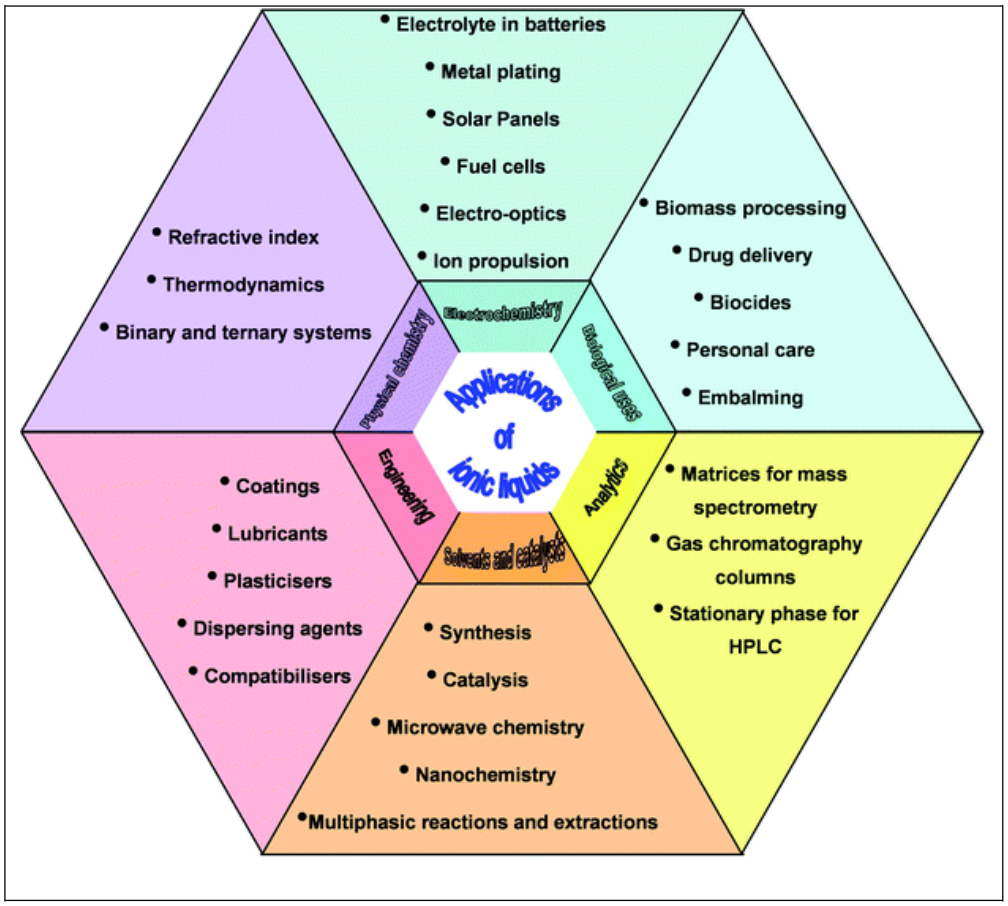


Figure 1.5: Pictorial representation for applications of ILs.

Considering the scope of this thesis, some of the main synthetic applications are briefly discussed in Section 1.7 below.

General Properties of Ammonium ILs

Ammonium ILs possess lot of interesting properties including the engineering features and laboratory easy applications, such as, potential solvent for CO_2 absorption, removal of SO_2 from natural gas, electro generate of cation radical, high conductivity agents, identification of degradation products, tunable phase behavior, distillable agent, biodegradable materials and their application in electrochemical fields. Compared with Imidazolium-based ILs, quarternary ammonium-based ILs possesses high solubility in water, lower thermal stability. The alkyl ammonium based ILs exhibit a higher viscosity than the Imidazolium based ILs with the same anion. This variation of viscosity of pure ILs changes with a variation in the structure, anion effect and intra-molecular interactions. Vander Wall‟s interactions due to the presence of a long alkyl chain lead to higher viscosities, whereas, the decrease in viscosity depends on the solvent added and the extent of resulting dissociation into ion.

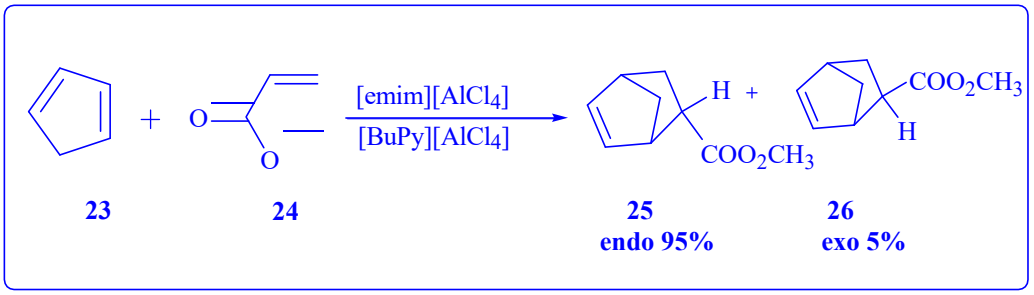
Although ILs research is most promising in recent years, the main drawbacks of this research is high cost of the precursors to synthesis of Imidazolium, pyridinium and other ILs. Whereas, the precursors of ammonium based ILs are still low cost, so the sustainability of ILs research using ammonium based ILs are maximum compared to the Imidazolium based ILs.

Importance of ionic liquids in organic synthesis:

Diels-Alder Reaction:

Diels-Alder reaction is a powerful tool in synthetic chemistry when building a molecule scaffold. The reaction was developed in 1928 by O. T. H. Diels and K. Alder and has been extensively studied in nonpolar solvents and water. Dramatically, reaction rates and stereoselectivities were found to be enhanced in water and the results were attributed to hydrogen bonding between transition states and aqueous media [72]. The reactions were also performed in other polar and environmentally friendly solvents (i.e. ionic liquids) to study their effects on stereoselectivities.

The first Diels-Alder reaction in IL was reported in 1989, which was performed in $[EtNH_3][NO_3]$ by Jaeger and Tucker [73]. Promising results were obtained when C. W. Lee carried out cycloaddition of cyclopentadiene (**23**) and methyl acrylate (**24**) (Scheme 1.1). Improved reaction rates, and selectivities were obtained in [emim][Cl] and [BuPyr][Cl] compared to traditional solvents [74].

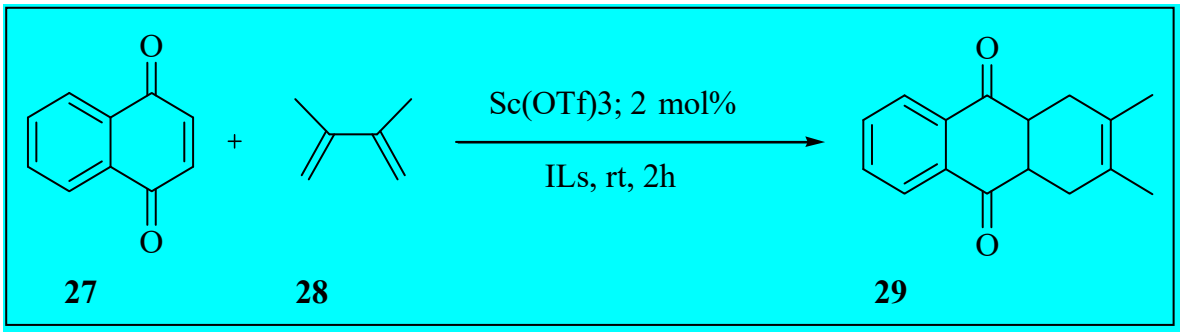


Scheme 1.1: Diels-Alder reaction of cyclopentadiene and methyl acrylate.

Furthermore, the authors studied chloroaluminate derivatives of the same ILs as reaction media and obtained even higher reaction rates and with ***endo:exo*** (19:1) selectivity. In some cases, ILs can reverse the selectivity obtained in traditional solvents [75]. Welton *et al*. [76] investigated the effect of the anion on the selectivity of ***endo:exo*** products and found a clear trend for [bmim] salts. The selectivity decreased in the order $[CF_3CO_2]^-$>$[NTf_2]^-$ >$[OTf]^-$ >$[BF_4]^-$>$[PF_6]^-$ which is in agreement with the E_T^N values evaluated for these salts.

Studies have already revealed that when Lewis acids are being used as catalyst, Diels-Alder reactions produce enhanced yields and selectivities. Hence chloroaluminate, [75] chlorozincate [77] and chloroferrate salts of ILs were also studied. The most common Lewis acid is $Sc(OTf)_3$, being a highly active catalyst for these reactions. In 2001, Song *et al*. [78] reported cycloaddition of a variety of substrates in [bmim] ILs using 0.2 mol% $Sc(OTf)_3$ at 20 °C (Scheme 1.2).They achieved quantitative yields (>99%) with almost completestereoselectivity for the ***endo*** product (Table 1.9).

Table 1.10 shows the results of cycloaddition between 1, 4-naphthoquinone (**27**) and 2, 3-dimethylbuta-1, 3-diene (**28**).



Scheme 1.2: Cycloaddition of 1, 4-naphthoquinone and 2, 3-dimethylbuta-1,3-diene.

Table 1.9: Results for Diels-Alder reaction.

Entry	**Solvent**	**Yield 29** (%)
1	CD_2Cl_2	22
2	[bmim][PF_6](0.1 eq.) + CD_2Cl_2	46
3	[bmim][PF_6](0.5 eq.) + CD_2Cl_2	85
4	[bmim][PF_6](1.0 eq.) + CD_2Cl_2	>99
5	[bmim][PF_6]	>99
6	[bmim][SbF_6]	>99
7	[bmim][OTf]	>99
Reaction conditions: 3 mmol 2,3-dimethylbuta-1,3-diene (28), 1 mmol 1,4-naphthoquinone(27), 0.2 mol% Sc(OTf)3, 1 mL solvent, 20 °C, 2 h		

Chiral induction was investigated using chiral ionic liquids (CILs) (**30**) and (**31**) as solvents (Fig. 1.6).

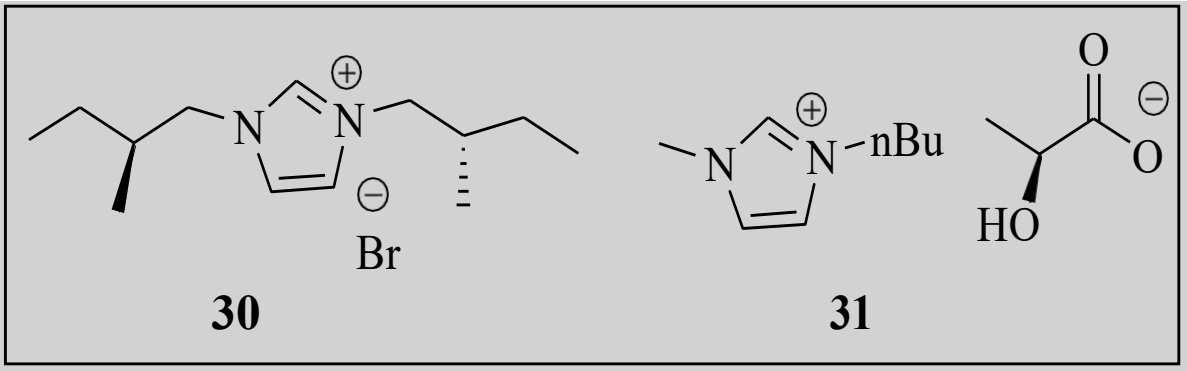
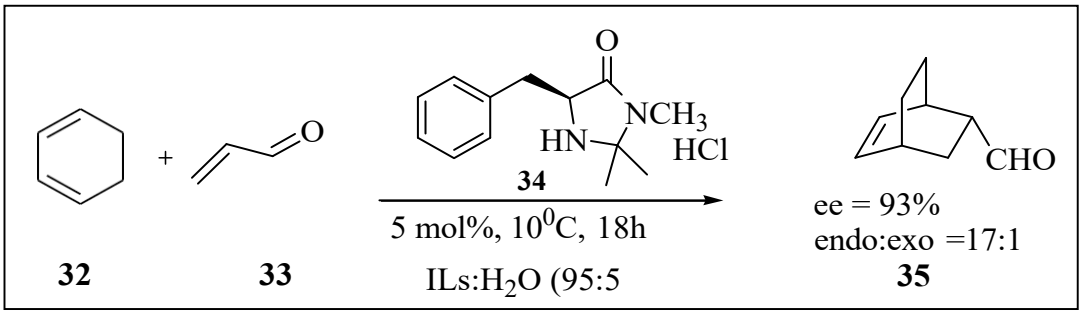


Figure 1.6: Chiral ionic liquids.

When (**30**) was employed in the reaction, < 5% ***ee*** was achieved [79] whereas (**31**) gave 4.4:1 diastereoselectivity with no significant enantioselectivity [80]. Although not with CIL, notable chiral induction was observed, in the cycloaddition of cyclohexadiene (**32**) and acrolein (**33**) using a chiral catalyst (**34**) immobilised in [bmim][PF6] or [bmim][SbF_6] with 5 v/v% water (Scheme 1.3) [81].



Scheme 1.3: Cycloaddition using chiral catalyst in ILs.

Moderate yields (70-80 %) and selective *endo:exo* ratio (17:1) with 93% of ***ee*** was obtained. Authors attribute improved results to critical role of water in iminium ion hydrolysis during catalytic cycle [81].

Hydrogenation:

Hydrogenation is often referred to as a 'green' reaction in present day chemistry. A number of solvents including ILs have been employed in hydrogenations with the first publication of a hydrogenation in ILs reported by Chauvin *et al.* [82] in 1995. 'Osborn complex' [$Rh(nbd)(PPh_3)_2$][PF_6] (nbd=norbornadiene) (**36**) was dissolved in [bmim] ILs with weakly coordinating anions (e.g. PF_6^-, BF_4^-, SbF_6^-) for the hydrogenation of 1-pentene at 30 °C. Independent of the limited solubility of the reactants, the reaction rates in [bmim][SbF_6] were five times faster than in acetone, with improved product selectivity [82b].

The Rh-catalyst was immobilized in the IL without any structural modification, which is generally required in the case of other polar solvents. Secondly, only 0.02% leaching of

catalyst was observed in the organic phase. Furthermore, authors investigated the hydrogenation of cyclohexadiene (**32**) with the same conditions and observed 96% conversion with 98% product selectivity to cyclohexene. Product selectivity was attributed to low solubility of cyclohexene in [bmim][SbF_6], so that further reduction is restricted. Many other researchers obtained similar results on several substrates including 1, 3-butadiene, 1, 4-cyclooctadiene and benzene [83]. Different metal catalysts have been reported to be successful for hydrogenation in ILs, for instance, Rh and Co-catalysts for olefins, [84] Ru-catalysts for aromatic compounds [85] Stereoselective hydrogenation of sorbic acid was successfully carried out by Steines *et al*. [86] in [bmim][PF_6] at 40°C with [RuCp*(η^4-sorbic acid)][OTf] (**36**) (Fig. 1.7) as a catalyst.

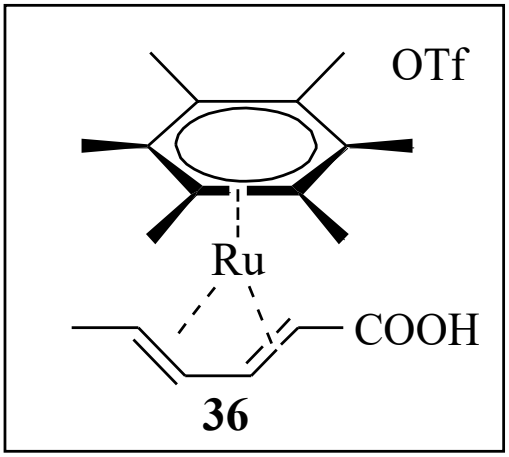
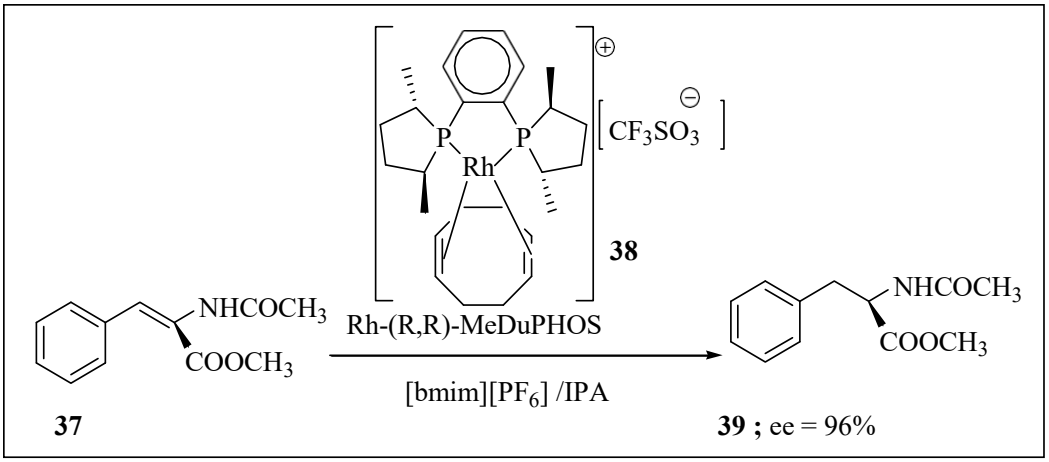


Figure 1.7: [RuCp*(η4-sorbic acid)][OTf].

The product, ***cis***-3-hexanoic acid was obtained with up to 93% selectivity with moderate conversion (52%). Increased H_2 pressure lead to reduced selectivity **(*cis/trans*)** whereas the effect of temperature was found to be less pronounced.

Asymmetric hydrogenation is an important reaction in organic synthesis which is used to synthesize chiral molecules. The application of ILs as reaction media in hydrogenation provides the advantage of a recyclable catalytic system. Reduction of α-acetamidocinnamic acid (**37**) was carried out in [bmim][PF_6]/IPA mixture using Rh-DuPHOS (**38**) at 25 °C and 2 bar of H_2 (Scheme 1.4) [87].



Scheme 1.4: Asymmetric hydrogenation in [bmim][PF_6]/IPA.

Moderate to good yields (83-60%) and 96% enantio-selectivity was achieved. Although these results are slightly lower than obtained in 2-propanol, the immobilised catalyst is far more stable towards oxidation in IL.

Table 1.10: Results for asymmetric hydrogenation of 37 to 39

Entry	**Conversion** (%)	***ee*** (%) (***R***-isomer)
1	83	96
2 (1st recycle)	64	96
3 (2nd recycle)	62	95
4 (3rd recycle)	60	94
5 (4th recycle)	58	94
Reaction conditions: ***7 g IPA + 5 g [bmim][PF_6], 25 °C, 2 bar of H_2, 20 min.***		

No significant drop in enantio-selectivity was observed until the fourth recycle whereas conversion showed a considerable decrease (Table 1.10). The major problem encountered in hydrogenations using ionic liquids is low H_2 solubilities compared to traditional solvents [88, 89]. Table 1.11 shows the H_2 gas solubility in several solvents.

Table 1.11: Hydrogen concentration in common solvents and selected ILs[a] at 298 K and atmospheric pressure.

Solvent	**H_2**[mM]	**Solvent (ILs)**	**H_2** [mM]
Water	0.81	[bmim][BF_4]	0.86
Methanol	3.75	[bmim][PF_6]	0.73
Ethanol	2.98	[bmim][SbF_6]	0.93
Benzene	4.47	[bmim][OTf]	0.97
Toluene	3.50	[bmim][NTf_2]	0.77
Cyclohexane	3.63	[bmim][CF_3CO_2]	0.98
		[hmim][BF_4]	0.79
		[omim][BF_4]	0.62

The problem can be solved by carrying out reactions at elevated temperatures as at higher temperature the viscosity of the IL decreases, and mass transfer effects become less significant [90]. A similar technique was applied by Dyson *et al*. [91] where they demonstrated a biphasic hydrogenation system consisting of catalyst immobilized in [omim][BF_4] and substrate, 2-butyne-1,4-diol dissolved in water (Fig. 1.8).

At room temperature, the phases were immiscible; however, at the reaction temperature of 80 ºC homogeneity was attained.

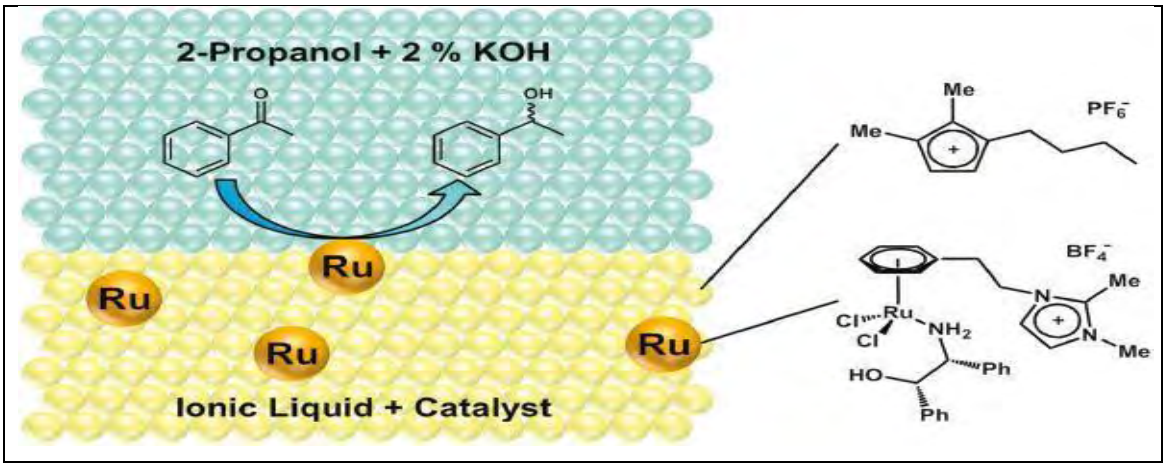


Figure 1.8: Hydrogenation under reversible dual-single phase solvent system

The reaction was carried out under 60 atm. of the H_2 gas with facile separation of the reduced products from the catalyst/IL phase being achieved simply by cooling the reaction (Fig. 1.5). Products dissolved in the aqueous layer were isolated and reuse of the IL/catalyst system demonstrated.

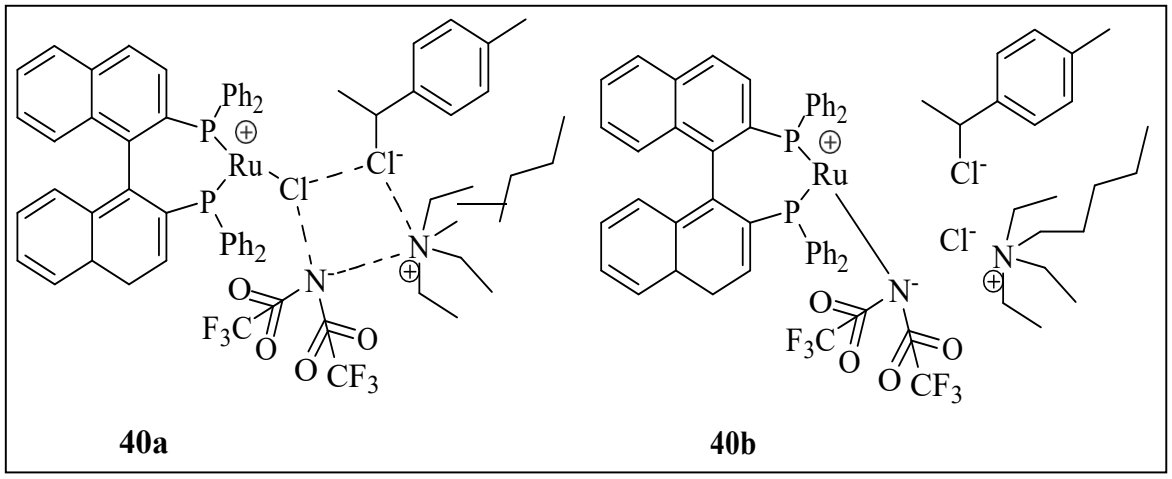


Figure 1.5: Proposed ‘‘weak’’ catalyst-IL ionic pairs interaction.

Anions are believed to have a considerable effect on the reaction rates by defining the physical properties of IL, and also via stabilisation of the catalyst [92, 93]. T. Floris proposed that stabilisation occurs through structural modification of the active catalytic centre with the anionic pair as shown in Fig. 1.16. Similar stabilisation was observed for Wilkinson's catalyst by chloroaluminate anion, but these ILs are rarely used for hydrogenations due to their tendency to polymerise olefins [93].

Oxidation:

Ionic liquids were initially developed for applications in electroplating and batteries due to their wide electrochemical window allowing their usage in redox reactions [94]. The first metal catalysed oxidation in an IL was reported in 2000, [95] where *p*-substituted benzaldehydes were oxidised to corresponding carboxylic acids using nickel (II)acetylacetonate [Ni(acac)$_2$] and molecular oxygen in [bmim][PF_6] at 60 °C. Common oxidants utilised in ILs are tabulated below (Table 1.12).

Table 1.12: Oxidants currently used in ILs.

Oxidants	Comment
O_2	Cheap and environment friendly, low solubility in ILs.
aq. H_2O_2	Environment friendly, water may be unwanted in some cases.
aq. NaOCl	Cheap & environment friendly, water may be unwanted in some cases.
*t*BuOOH	Relatively cheap, available as both aq. and anhydrous solutions.
$PhI(OAc)_2$	Relatively expensive but easy to handle.
$H_2NCONH_2.H_2O_2$	Water free peroxide source, readily soluble in many ILs.
N-morpholine-*N*-oxide	Expensive, residual morpholine may be a problem.

For a clean and green synthesis, oxidants should produce non-toxic by-products, or ideally water. Earle *et al*. [96] developed an oxidation method for alkylaromatic compounds using nitrate based ILs. Such ILs are termed as 'task specific ionic liquids' **(TSILs)** where IL is employed as media and reagent. 70-90% yields were obtained in these reactions. Substituted benzyl alcohols were oxidised to their corresponding carbonyl compounds, using NaOCl and guanidium IL (**41**) (Fig. 1.10), at pH~8-9 [97].

A guanidium based IL was chosen for this reaction due to its greater stability under basic conditions. In this case, the IL also works as a phase transfer catalyst with 65-99% reaction yields obtained. Similar oxidations were attempted with IBX and DMP using [bmim][BF_4] as a solvent to achieve > 90% yields [98].

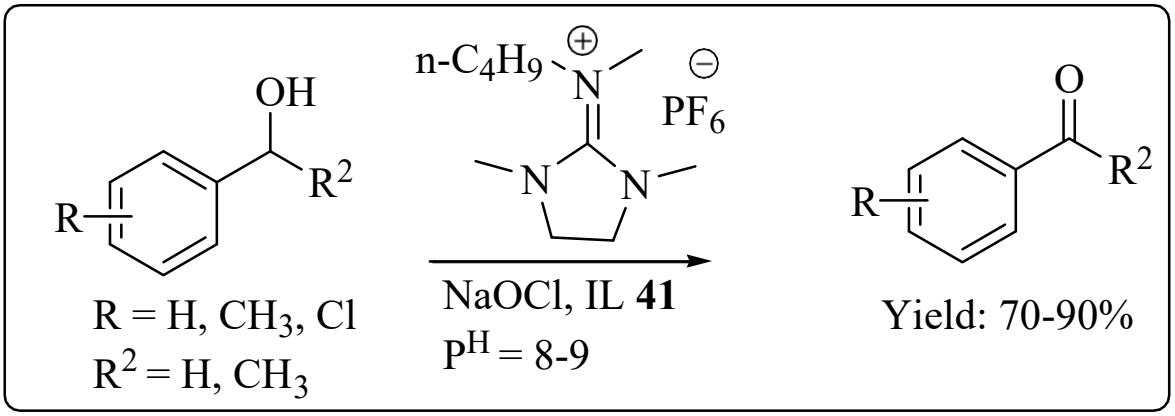


Figure 1.10: Guanidium IL for oxidation.

K. Tong *et al*., [99] carried out epoxidation reactions using styrenes, pinene, norbornene in [bmim][BF_4] with tetramethylammonium bicarbonate and manganese (II) sulphate as a catalyst at rt. The reaction worked successfully, affording 98-99% yields and the catalytic system could be recycled without loss in activity up to 5 times. Asymmetric epoxidations are extensively studied with ILs. As the Jacobsen epoxidation can occur even in unfunctionalised olefins, this is one of the popular methods of epoxidation. Song *et al*. [100] investigated the biphasic epoxidation of chromenes with chiral Mn^{III} (salen) (**42**) (Fig. 1.11) and NaOCl in mixture of [bmim][PF_6] and CH_2Cl_2 (1:4 ratio).

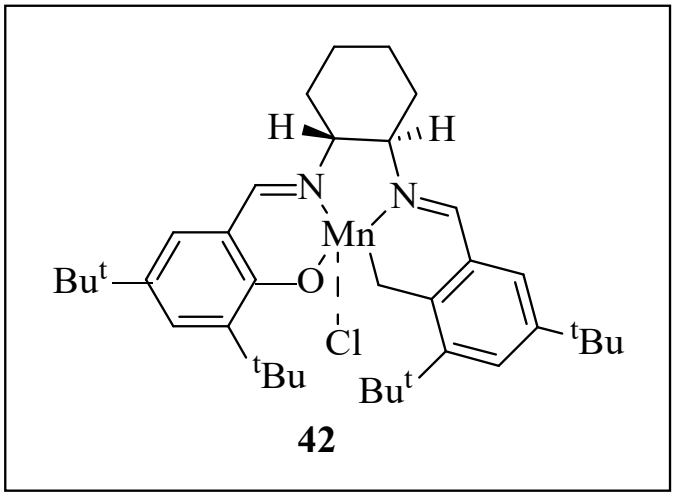
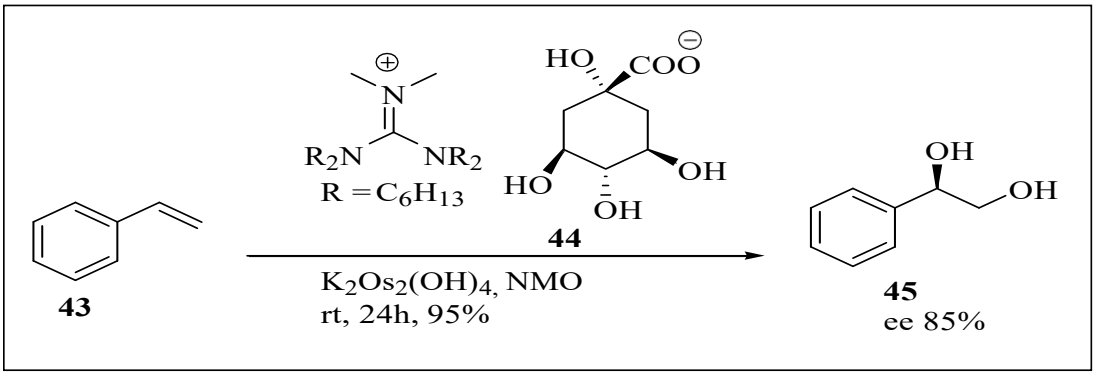


Figure 1.11: Mn^{III}-salen complex.

The authors found an enhancement in catalytic activity upon addition of IL to DCM. With the IL, 86% conversion was observed in 2 h, whereas it took 6 h for same conversion without the IL. In both cases 96% enantiomeric excess was observed which reduced by only 6% after the 5th cycle. Recently, asymmetric epoxidation of styrene derivatives was studied using 10 mol% silica supported Mn^{III}(salen) complex and NaOCl in [bmim][X]-DCM (X=PF_6, BF_4)

mixtures with NH_4OAc as a co-catalyst [101]. After 2 h, 45-82% yields with 65-95% ***ee*** were obtained. The outcome of the process was the catalytic system could be re-used up to 4 times without any leaching of the catalyst. Chiral building blocks available from Nature are often applied for chiral induction. Interestingly, guanidium quinate (**44**), was synthesized and employed as a solvent in the asymmetric dihydroxylation of styrene (**43**) (Scheme 1.6) and 1-hexene [102].



Scheme 1.6: Chiral induction by IL in asymmetric dihydroxylation.

The catalytic system utilised was $K_2OsO_2(OH)_4$/NMO and reactions were performed at rt. Remarkably, 85% enantiomeric excess and 95, yield was obtained when styrene was the substrate. A similar yield (92%) was found using 1-hexene, although the *ee* decreased to 72%.

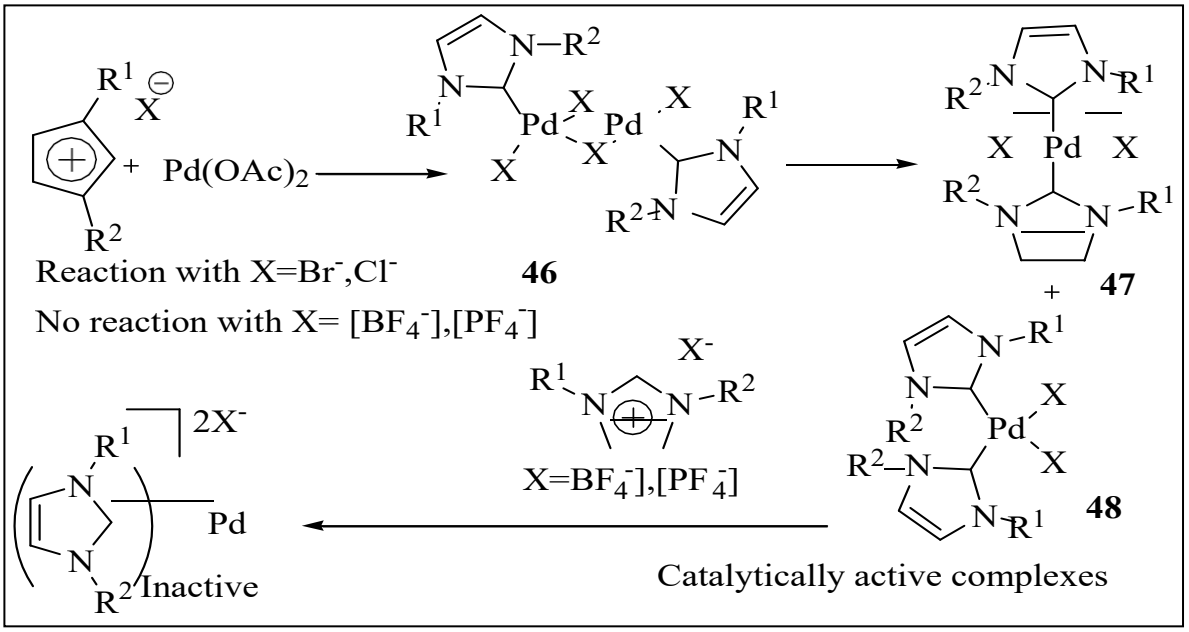
Carbon-carbon coupling reactions:

Coupling reactions have had a huge impact on synthetic chemistry over the last thirty years. Large carbon scaffolds can be built using metal catalysed C-C coupling reactions, generally in excellent yields. Hence, by appreciation of the usefulness of the three main Pd-catalysed coupling reactions, a Nobel Prize (chemistry) was awarded to their inventors in 2010. Mannich, Heck, Suzuki, Negishi, Stille and Sonogashira couplings present easy procedures to serve the purpose of C-C linkage, usually with low catalyst loading (2-5 mol%). Theionic liquids possessing high polarity, density and viscosity interact with metal catalysts in a different way to conventional solvents. The hydrogenation section 1.8.2 (***vide supra***) shows that ionic liquids can be employed in metal catalysed reactions with successful recycling. C-C coupling reactions in ILs were studied by many researchers to investigate the effect of the IL-catalytic system on the yield, enantio-selectivity and stability of the catalytic system.

Heck coupling.

Imidazolium based ILs have been studied in detail for past two decades. Their utility in Pd-catalysed reactions, whether hydrogenation or C-C coupling reactions, was investigated

revealing that at high temperatures under basic condition imidazolium moieties form carbine complexes with palladium [103]. Mostly this reduces the yield of the reactions but in some cases better results were observed. The carbene complexes (**47**, **48**) were formed and found to give better results than the original palladium catalyst during the coupling of various aryl halides and acrylates (Scheme1.7) [104].



Scheme 1.7: Formation of Pd-carbene complex.

Reactions in [bmim][Br] gave quantitative conversions (100%) with~99% selectivity to the ***trans*** product. Investigation revealed that complex formation takes place only in the presence of halides and when [bmim][BF_4] was employed in the reaction, no carbene complex was formed giving poor conversions. A range of Pd catalysts were tested for their catalytic activity in the coupling of styrene (**43**) and chlorobenzene [105].

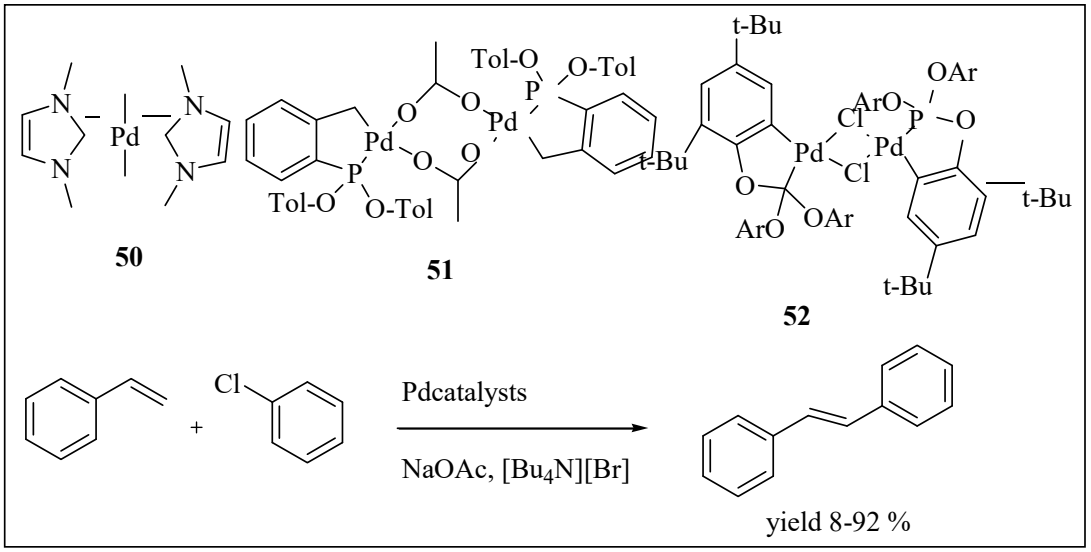


Figure 1.12: Pd-carbene complexes for Heck coupling.

Pd-carbene complexes that were used are shown in Fig. 1.12. The results for these reactions are shown in Table 1.13. Provided that the chlorobenzene possesses low reactivity towards Heck coupling, even in conventional solvents (especially when $PdCl_2$ and $Pd(OAc)_2$ used as catalysts) tetrabutylammonium bromide (TBAB) has yielded satisfactory results.

Table 1.13: Heck coupling of chlorobenzene and styrene in [Bu_4N][Br].

Catalyst	Yield (%)	
	DMF	[Bu4N][Br]
$PdCl_2$	0	50
$Pd_2(dba)_3$	2	8
$Pd_2(dba)_3$ + 2 eq. P(*t*Bu)$_3$	72	92
$Pd(OAc)_2$ + 3 eq. P(*o*-Tol)$_3$	29	46
$Pd(PPh_3)_4$	17	65
(**51**) + 5 eq. [$AsPh_4$][Cl]	41	84
(**50**)	3	51
(**52**)	5	49
Reaction conditions: Styrene (1.5 eq.), NaOAc(1.2 eq.), Pd (2 mol%), 150°C,18 h		

Recently, ligand free Heck arylation was successfully demonstrated by Petrvic *et al*. [106]. They synthesized triethanolammonium acetate to employ ligand-free Heck coupling. The reaction was carried out with iodo/bromobenzene and alkylacrylates using 2 mol% $PdCl_2$ and [TEA][OAc] at 110°C with quantitative yields (>90 %).

The authors concluded that the IL in this case acted more than a medium and worked as a base, precatalyst, and mobile support for the active Pd species. Further studies revealed that

cations and anions were not distinctive as such still molecule showing high dipole moment and also behaved like a molecular solvent due to strong hydrogen bonding (Fig. 1.13).

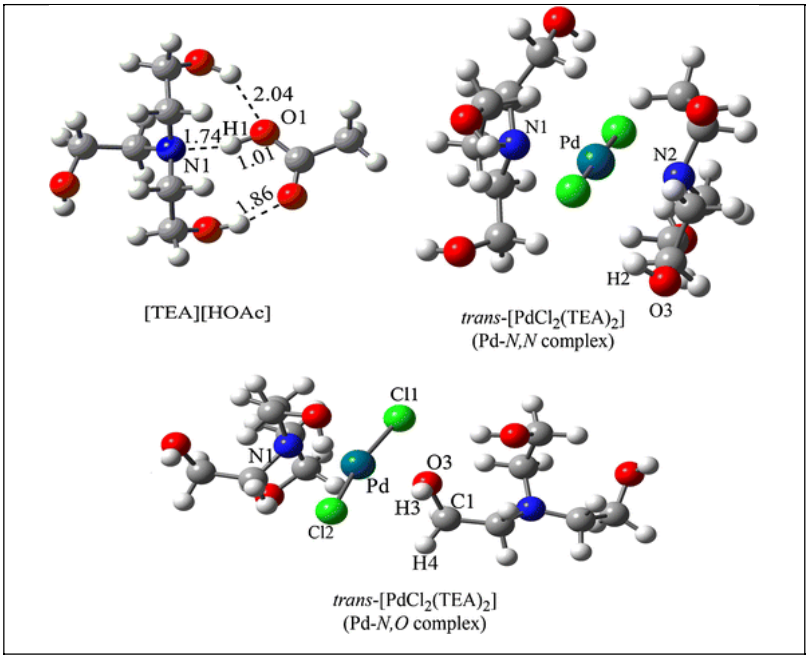
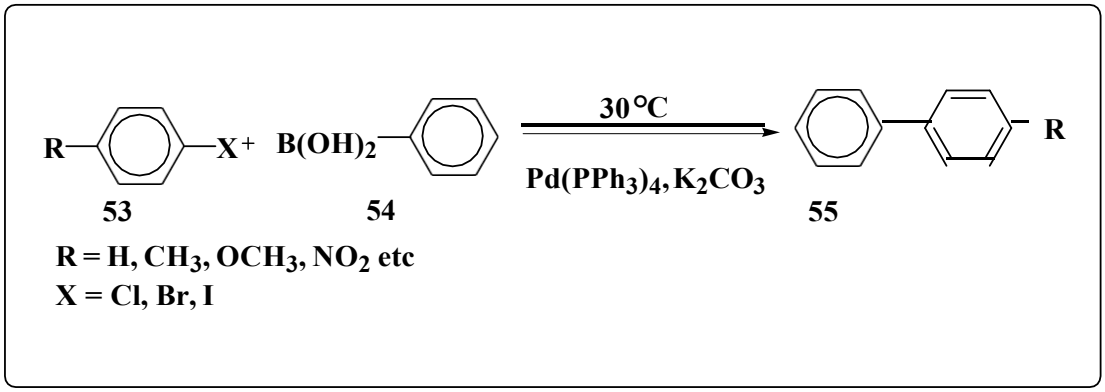


Figure 1.13: X-ray models of triethanolammonium acetate and it'sPd-complex; (leftintramolecularH-bonding, right-precatalyst)

Suzuki coupling:

Coupling of aryl/vinyl boronic acid with aryl/vinyl halide catalyzed by a palladium complex is known as Suzuki coupling [107]. This reaction enables the linkage of aryl, vinyl, benzyl, allyl and alkyl groups (cf Heck coupling). Several papers have described the Suzuki reaction using [bmim] ILs and Pd catalysts bearing phosphanes, [108] nitrogen compounds [109] and carbenes [110].

The reaction of bromobenzene with phenylboronic acid in benzene, catalysed with $Pd(PPh_3)_4$ and K_2CO_3, gave a 88% yield in 6 h, while the same reaction in [bmim][BF_4] gave a 93% yield of the desired product in 10 minutes with a high turnover number [111]. Microwave/ultrasound assisted reactions are generally clean and can be put forward under 'green' chemistry due to their environment friendly energy efficiency. Shrinivasan *et al.* [109a] performed coupling of a range of halobenzenes (**53a-k**) with phenylboronic acid (**54**) in [bbim][BF_4]/MeOH mixture under ultrasonic irradiation at 30 °C (Scheme 1.8).



Scheme 1.8: Sono-chemical Suzuki reaction in [bbim][BF_4]/MeOH.

Palladium acetate was employed as a catalyst and 40-93 % yields were obtained as shown in Table 1.14.

Table 1.14: Ultrasonic Suzuki cross-coupling of halobenzenes with phenyl boronic acid in [bbim][BF4]/MeOH.

No.	**Substrate**	**Time** (min)	**Yield** (%)
1	Iodobenzene (**53a**)	20	92 (**55a**)
2	4-Methoxyiodobenzene (**53b**)	20	93 (**55b**)
3	4-Chloroiodobenzene (**53c**)	30	85 (**55c**)
4	4-Nitroiodobenzene (**53d**)	30	82 (**55d**)
5	Bromobenzene (**53e**)	45	82 (**55e**)
6	4-Methoxybronobenzene (**53f**)	10	85 (**55f**)
7	4-Nitrobromobenzene (**53g**)	20	90 (**55g**)
8	Chlorobenzene (**53h**)	60	42 (**55h**)
9	4-Nitrochlorobenzene (**53i**)	30	65 (**55i**)
10	4-Chlorotoluene (**53j**)	60	52 (**55j**)
11	2,4-Dinitrochlorobenzene (**53k**)	90	42 (**55k**)
Reaction conditions*: *0.5 g [bbim][BF_4], 1 mL MeOH, 0.001 g $Pd(OAc)_2$			

To achieve better immobilisation of Pd complex in ionic liquid, Dyson *et al*. [112] synthesized pyridine;um based ILs containing the coordinating nitrile functional group.
Coupling of iodobenzene (**53a**) and phenylboronic acid (**54**) was carried out in these ILs. The nitrile groups coordinate with $PdCl_2$ forming a pre-catalyst (Fig. 1.14) and good yields (81-

88%) were achieved with the catalyst found to be air stable. Leaching of the catalyst during work-up was reduced compared to [BuPy][NTf_2].

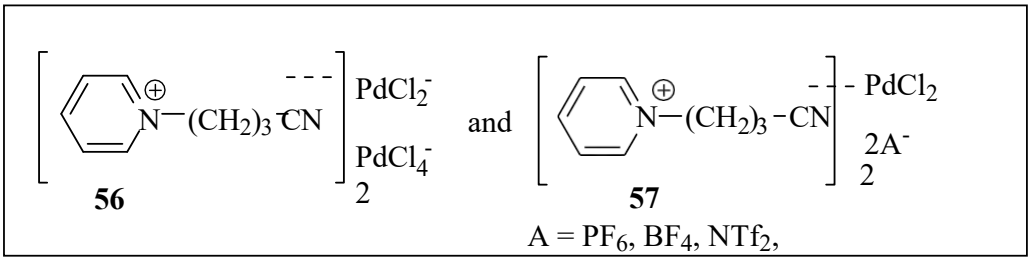
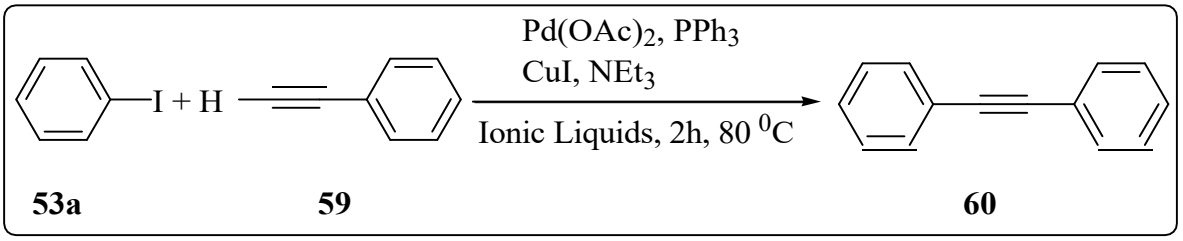


Figure 1.14: Interaction between nitrile functionalised IL and $PdCl_2$.

Sonogashira Coupling:

Sonogashira coupling is recognized as a powerful synthetic tool for the formation of asymmetrically substituted acetylenes [113]. The reported publications using ILs show improved results compared to traditional solvents [114-116]. Kmentova *et al.* [114] performed coupling of iodobenzene (**53a**) and phenylacetylene (**59**) in various imidazolium based ILs with $Pd(OAc)_2/PPh_3$ as a catalyst, CuI as a co-catalyst and NEt_3 (TEA) as a base (Scheme 1.9).



Scheme 1.9: Sonogashira coupling of iodobenzene and phenylacetylene.

The results obtained are tabulated below (Table 1.15).

Table 1.15: Yields of Sonogashira coupling in different ILs.

Entry	Ionic liquid	Yield (%) (**60**)
1	[bmim][PF_6]	97
2	1st recycle	93
3	2nd recycle	67
4	3rd recycle	58
5	[bmim][BF_4]	99
6	[hmim][PF_6]	95
7	[hmim][BF_4]	96
8	[bbim][BF_4]	97
Reaction condition*: *4 mol % $Pd(OAc)_2$,4 mol% CuI, 0.4 mL TEA, 80 °C,2h		

Excellent yields (>90 %) were obtained for imidazolium ILs and experiments with recycled catalyst showed a gradual decrease in yield which was due to catalyst leaching during workup. Many attempts have been made to carry out coupling without Cu catalyst because in some of the cases Glaser-Hay coupling can occur under Sonogashira conditions giving rise to unwanted homo coupling products [117]. In 2002, Fukuyama *et al*. [118] carried out coupling of several aryl iodides and substituted acetylenes in [bmim][PF_6] with 5 mol% $PdCl_2(PPh_3)_2$ and Hünig's base.

The authors obtained 85-97% yields despite the absence of Cu catalyst. Often coupling reactions are carried out at higher temperature, in the presence of base which can cause degradation or hydrolysis of the ionic liquid. Hence in such cases, reaction conditions demand robust ILs that can facilitate the reaction. Recently, Harjani and co-workers [119] synthesized nicotinate ester based ILs with the purpose to achieve stability for hydrolysis.

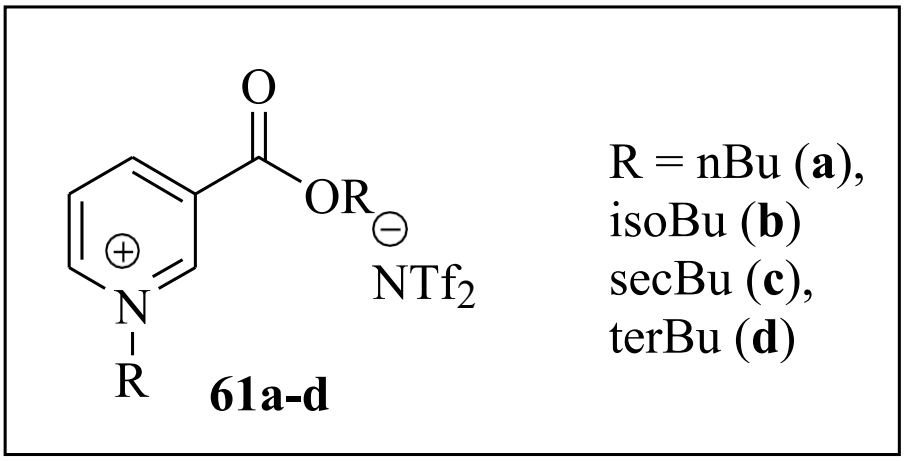


Figure 1.15: Nicotinate based ILs.

Coupling was carried out with phenyl acetylene (**59**) and different aryl iodides (including **53ab** and **53d**) in ionic liquids (**61a-d**) (Fig. 1.15) using $PdCl_2$ and TEA under ultra-sound irradiation. 78-93% yields were obtained in these reactions in accordance with expected reactivities of electron donating/withdrawing substituents on phenyl iodide.

Methods of Synthesis:

The ionic liquid synthesis, consists of two steps, first is the formation of the cation followed by the second step of anion metathesis to obtain the IL containing the desired anion. In some cases, anion metathesis is not needed, as the first step serves the purpose of both. For example, quaternarization of ethyl amine with conc. HNO_3 would give the final IL. Figure 1.16 illustrates the reaction scheme for dialkylimidazolium IL synthesis.

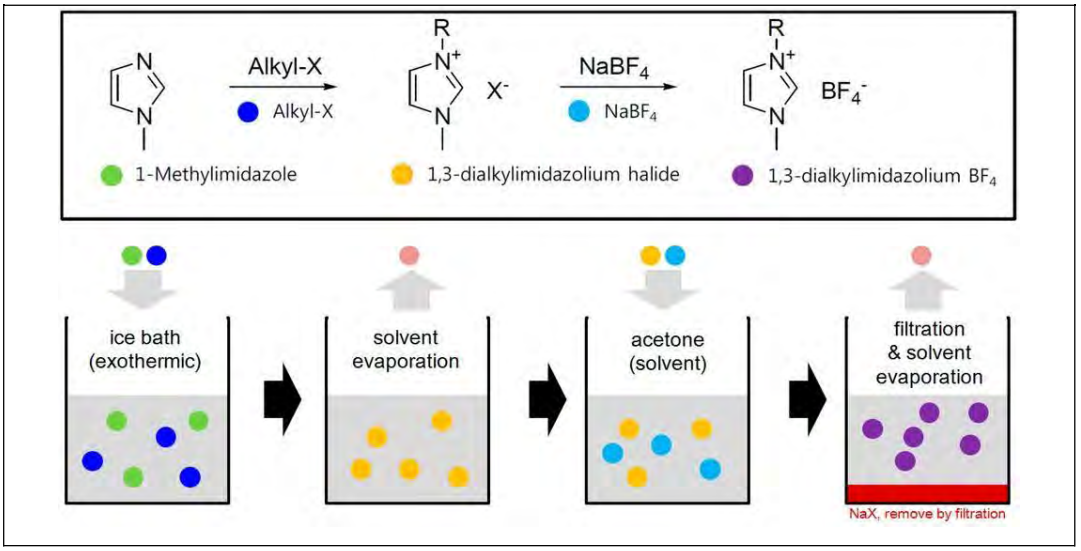


Figure 1.16: Synthetic route for imidazolium based ILs.

The formation of the cation can be carried out either via protonation with protic acid [120] or via quaternization of the amine, phosphine or ternarization of the sulphide most commonly using alkyl halide or dialkylsulphates. The alkylation process to form the halide salt has the advantages of (i) a wide range of cheap alkyl halides are available, and (ii) the substitution reactions occur smoothly at reasonable temperatures. Several types of amines, phosphines, and sulphides were tried in the preparation of ILs, some of them are shown in Fig. 1.17. Anion metathesis is needed as the halide anions obtained in the first step are often corrosive and the salts would be solid mostly. Hence metathesis is carried out to obtain an IL with an inert anion.

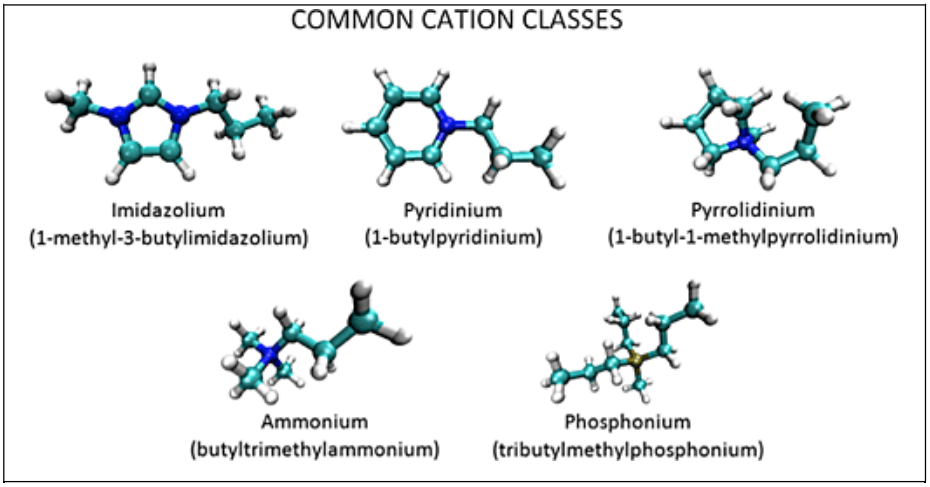


Figure 1.17: Cation diversity in the field of ILs.

The anion may affect the physicochemical properties of ionic liquid drastically. Different types of anions have been introduced and the combinations with several cations have been synthesized. K. Seddon predicted that there are a quintillion (10^{18}) number of compounds possible with the different combination of cations and anions [121]. Table 1.16 shows few papers which have been published over the years with different anions.

Table 1.16: Publications related to synthesis applications of corresponding anions

Sr. No.	Anions	Sr. No.	Anions
1.	BF_4^-[58]	16.	$ZnCl_3^-$[72]
2.	PF_6^-[64]	17.	$CuCl_2^-$[72]
3.	SbF_6^-[65]	18.	$SnCl_3^-$[72]
4.	$CH_3CO_2^-$[58]	19.	$N(EtSO)_2^-$[72]
5.	HSO_4^-[66]	20.	$N(FSO_2)^-$[72]
6.	NO_3^-[58]	21.	$C(CF_3SO_2)3^-$[73]
7.	NO_2^-[58]	22.	$CH_3SO_3^-$[72]
8.	$CF_3SO_3^-$[57]	23.	$N(CN)_2^-$[74]
9.	$(CF_3SO_2)_2N^-$[59]	24.	Halides[75]
10.	$CF_3CO_2^-$[57]	25.	$Al_2Cl_7^-$[72]
11.	$B(Et_3Hex)^-$[67]	26.	$Al_3Cl_{10}^-$[72]
12.	OTs^-[68]	27.	$Au_2Cl_7^-$[72]
13.	$AuCl_4^-$[69]	28.	$Fe_2C1_7^-$[72]
14.	$AlCl_4^-$[70]	29.	SbF_6^-[72]
15.	Carborane[71]		
anions (as 1-R-$CB_{11}H_6Cl_6^-$)			

Synthesis of Ammonium ILs:

The increasing interest of ILs and their recent widespread commercial availability, has resulted in further developments in their synthesis and purification [122]. A branch of ILs are protic ILs, which are easily produced through the combination of a Bronsted acid and Bronsted base. In fact, the story of ionic liquids is generally regarded as beginning with the first report on the preparation of protic ionic liquids ethylammonium nitrate in 1914 [123]. The same method has been applied to prepare other protic ionic liquids. The synthesis (Figure 2.3) of ILs generally can be divided into two steps: (i) formation of the desired cation, and (ii) anion exchange to form the desired product. In some cases, only the first step is required,

as with the formation of ethylammonium nitrate. In other case, where the desired anion could not be formed directly from the first step, the second step is needed which involves anion exchange. Protic ionic liquids are formed through the transfer of a proton from a bronsted acid to bronsted base. This leads to its distinguish features from the other ionic liquids, i.e., it has a proton available for hydrogen bonding. The protonation process to form desired protic ionic liquids possesses the advantages which among others are: (i) a wide range of cheap cation sources such as ammonium, and (ii) the protonation reactions generally spontaneous at room temperature. The most common method for the formation of such ionic liquids is simple mixing of the Bronsted acid to Bronsted base. The reaction is generally quite exothermic, which means that care should be taken when adding the reagents together. Although the products are relatively thermally stable, the build-up of excess local heat can result in decomposition and discoloration of the ionic liquid. This may be prevented either by cooling the mixing vessel or by adding one component to the other in small portions to allow the heat to dissipate naturally.

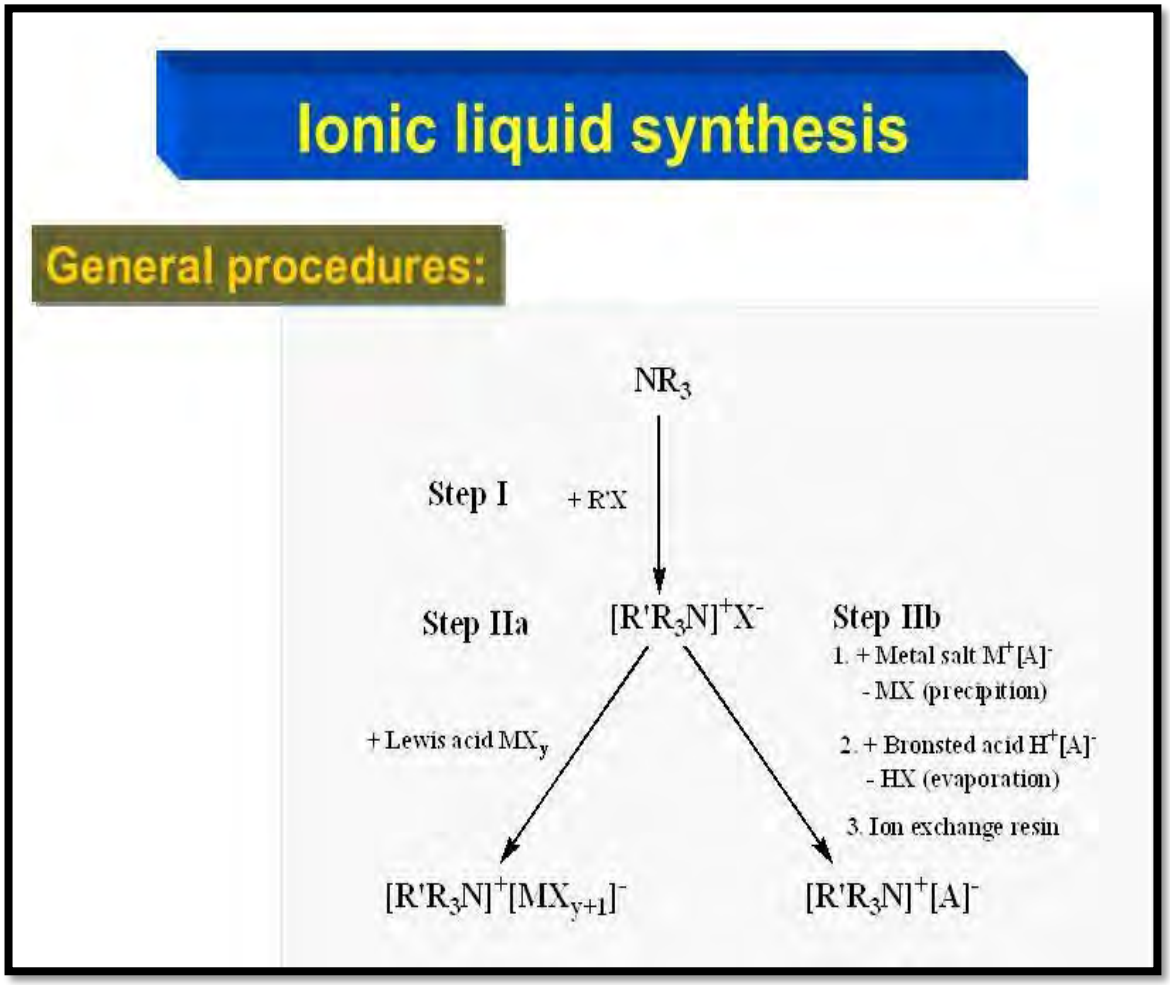


Figure 1.18: Synthetic pathway for Ammonium based ILs.

Chapter: 2

PRESENT WORK

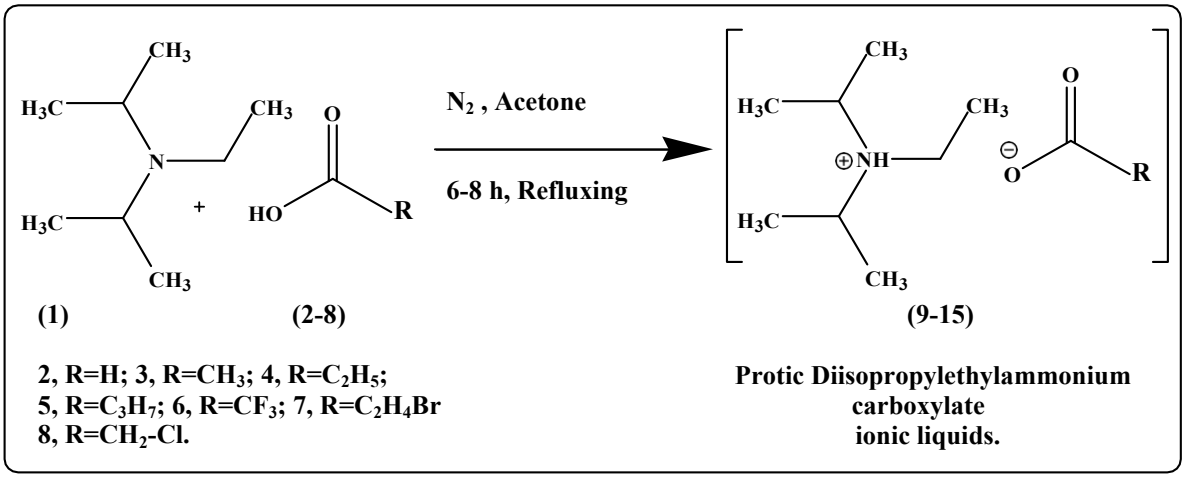
Title: SYNTHESIS AND CHARACTERIZATION OF protic AMMONIUN BASED IONIC LIQUIDS.

CHAPTER 2

SYNTHESIS AND CHARACTERIZATION OF PROTIC AMMONIUM BASED IONIC LIQUIDS

2.1 Rationale

Ionic liquids have a very wide spread application window in nuclear fuel reprocessing, solar thermal energy, electro-chemical devices, cellulose processing, etc. Along with physio-chemical properties, the low antimicrobial activities and high biodegradability of ILs have created a keen interest in researcher's minds to test their „green" applications in various fields.



Scheme 01: Synthetic route of protic Diisopropylethylammonium carboxylate ionic liquids.

Considering the lower antimicrobial properties of our first generation ILs and for the preparation of extensive series of ILs, it was planned to synthesize low toxic ionic liquids. *N,N*-Diisopropylethylammonium based ILs could to be synthesized by acid-base neutralization reaction of *N,N*-Diisopropylethylammonium with carboxylic acid under mild condition. These ionic liquids would be screened for antimicrobial toxicity and their applications in Mannich reaction and Esterification reaction were planned to carry out.

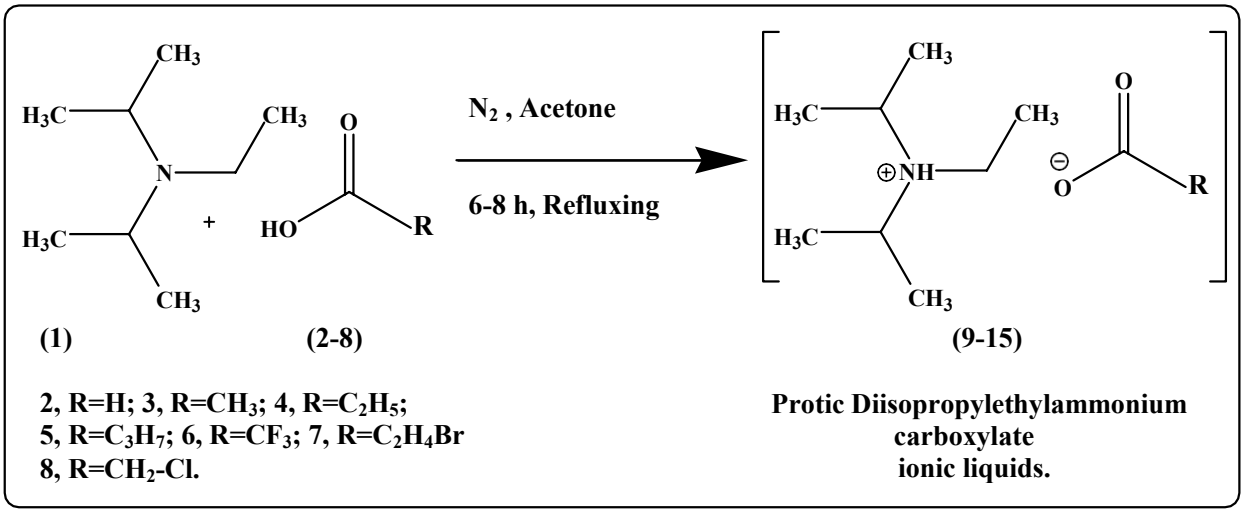
Experimental

The purity of synthesized ILs were maintained using vacuum oven and desiccators throughout the experimental period. The infrared (FT-IR) spectra of synthesized ILs are obtained on a Shimadzu Fourier-Transform Infrared spectrometer (Shimadzu IR Prestige21, Shimadzu Corporation). The ILs solid samples were mixed with dry KBr to make a thin plate for IR record. For liquid samples, blank KBr disc is swapped with little amount of ILs and put in the hole in radiation chamber. The FT-IR spectra produced had wave number range of 600-4000 cm^{-1}. In NMR, 5 to 10 mg of sample was dissolved in 0.7 mL of suitable solvent ($CDCl_3$, D_2O). The ^{1}H-NMR spectra were recorded at room temperature on Bruker Advance 400 MHz spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) references with Tetramethylsilane (TMS) as an internal standard. Multiplicities are abbreviated as s, singlet; d, doublet; t, triplet; and m, multiplet. Analytical thin-layer chromatography (TLC) was performed on pre coated silica gel 60F-254 (Merck, Germany) and the spots were visualized with UV light.

General procedure for the synthesis of diisopropylethyl ammonium based (ILs):

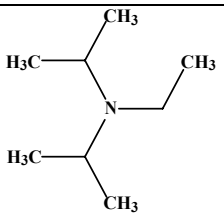
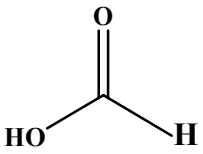
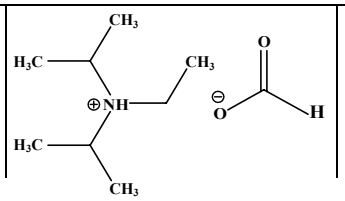
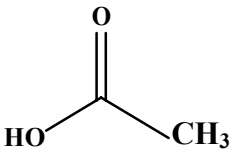
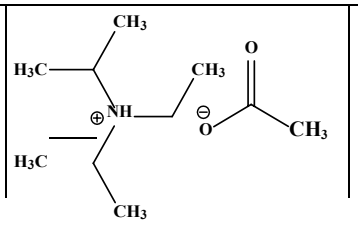
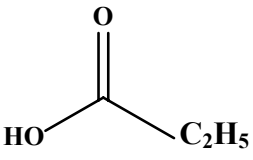
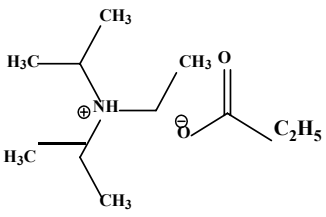
N,N-Diisopropylethylammonium based ILs have been synthesized by the acid-base neutralization reaction of *N,N*-Diisopropylethylamine with carboxylic acid, as shown in the **Figure: 3.1**.

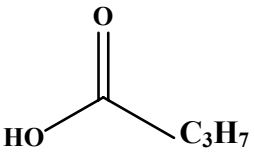
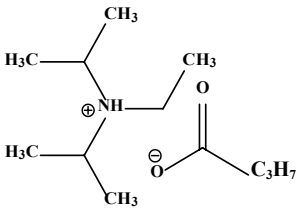
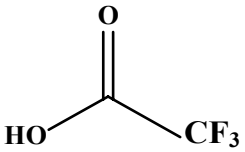
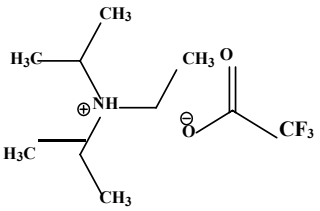
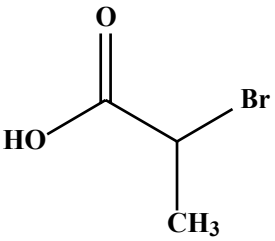
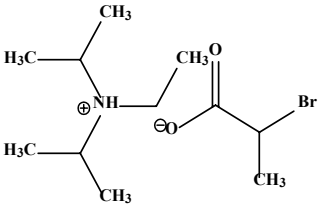
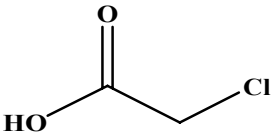
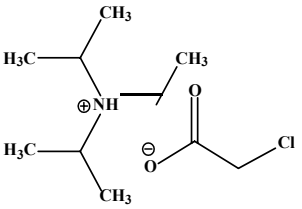
The stoichiometric quantity or equimolar amount of base (10 mmol) was added to solvent (acetone 5mL) into 100 mL round-bottom flask at 80 ºC. Then the flask was equipped with a teflon coated magnetic stir bar with condenser for refluxing. Then the reaction mixture was stirred for few minutes such that the substrate would be dissolved well. Then it was placed in ice-bath on magnetic stirring with reflux condenser under Nitrogen atmosphere. Then 10 mmol carboxylic acids were added in this mixture drop-wise over a period of 30 minutes. Then the reaction mixture was stirred for 4-6 hours. The progress of the reaction was monitored by thin layer chromatography (TLC), using the aluminum sheet coated with silica gel with MeOH: $CHCl_3$ as a mobile phase. Then the reaction mixture was cooled at room temperature. After that, the solvent was removed by rotary evaporator under reduced pressure and obtained colored or colorless ILs. For the further purification it was kept in vacuum oven at 90 ºC temperature for two days.



Scheme 01: Synthetic route of protic Diisopropylethylammonium carboxylate ionic liquids.

Table No.1: List of protic diisopropylammonium based ILs.

Entry	Organic base	Organic acid	Product (ionic liquids)	Yield %
01	 1	 2	 9	92
02	,,	 3	 10	87
03	,,	 4	 11	84

04	,,	 **5**	 **12**	**86**
05	,,	 **6**	 **13**	**95**
06	,,	 **7**	 **14**	**91**
07	,,	 **8**	 **15**	**93**

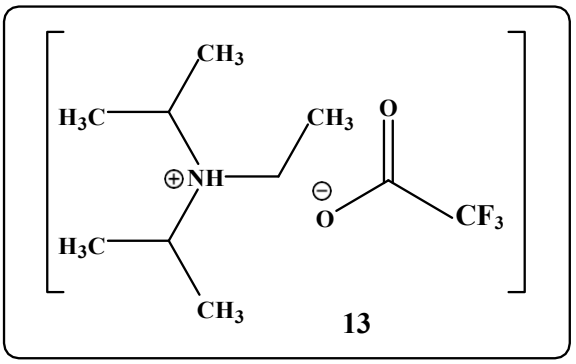
All the seven ILs were synthesized with equimolar amount of *N,N*-Diisopropylethylamine and organic acids, the details of all the reaction with the workup procedure were discussed in the following:

Synthesis of *N,N*-Diisopropylethylammonium TFA, K-IL: 05(13)

N, N-Diisopropylethylamine (10 m mol) and 5mL of acetone were charged into a 250 mL three necked round bottom flask equipped with a Teflon coated stir bar. Since the reaction was highly exothermic, so the flask was immerged in the ice-bath and the trifluoro acetic acid (10 m mol, 1.14g) was added dropwise to *N,N*-Diisopropylethylamine over a period of 30 minutes. Then the mixture was being stirred for 6 hours at 80 ^{o}C under nitrogen atmosphere.

The reaction was monitored by TLC using (MeOH : $CHCl_3$ = 1:3) solvent system. After completion the reaction, the mixture was cooled at room temperature and dried under the reduce pressure in vacuum and to obtained the title compound K-IL: 05**(13)** as a colorless liquid in 95% yield.

- Molecular weight : 289.27g/mol
- Density : 1.21 ± 0.05 g/cm^3
- Molecular formula : $C_{10}H_{20}NO_2F_3$
- FT-IR(υ_{max}KBr) : 3440, 2983.98, 1721, 1556, 1544, 1490, 1425, 1199, 1134, 1002, 758, 722, 607 cm^{-1} .
- ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 1.36 (t, J = 6.4 Hz, 3H, methyl), 1.42 (d, J = 7.6 Hz, 12H, methyl), 3.1 (quartet, J = 4.0 Hz, 2H, methylene), 3.55 (m, J = 2.8 Hz, 2H, methine), 10.55 (s, 1H, ammonium).



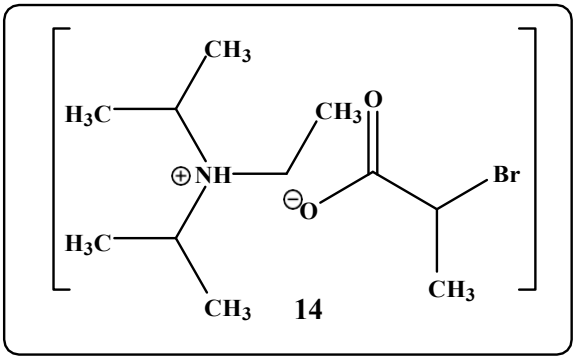
13

Synthesis of *N,N*-Diisopropylethylammonium 2-bromopropionate K-IL:06(14)

The compound **(14)** was prepared from *N,N*-Diisopropylethylamine (10 m mol) and 2-bromo propionic acid (10 m mol, 1.529g) according to previous method as a yellowish liquid in 91% yield.

- Molecular weight : 328.22 g/mol
- Molecular formula : $C_{11}H_{24}NBrO_2$
- Density : 1.24 ± 0.05 g/cm^3
- FT-IR(υ_{max}KBr) : 3436, 3061, 2959, 2358, 1774, 1633, 1536, 1486, 1460, 1305 1186, 1128, 1002, 860, 720, 608 cm^{-1}
- ^{1}H NMR (400 MHz, $CDCl_3$) ppm : 1.08 (t, J = 3.6 Hz, 3H, *methyl*), 1.26 (d, J = 6.8 Hz, 12H, *methyl*), 1.43 (d, J = 5.6 Hz, 3H, *methyl*), 3.12 (m, J =

3.2 Hz, 2H, *methylene*), 3.63 (m, J = 6.4 Hz, 2*H, methine*), 4.30 (quartet, J = 7.2 Hz, 1H, methine), 5.01 (s, 1H, ammonium).

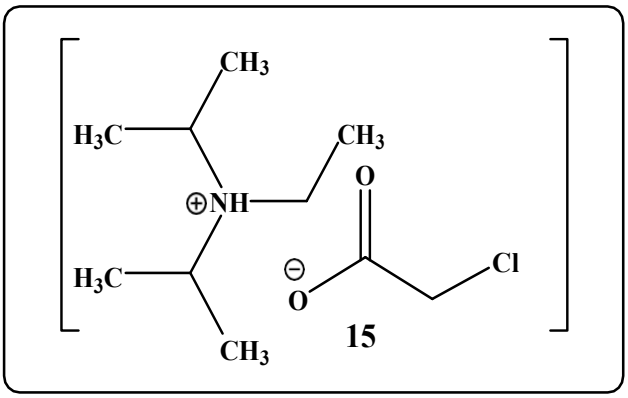


14

Synthesis of N,N-diisopropylethylammonium 2-Chloroacetate K-IL: 07(15)

The compound **(15)** was prepared from *N,N*-Diisopropylethylamine (10 mmol) and 2-chloroacetic acid (10 mmol, 1.14g) according to previous method in 93% yield.

- < Molecular weight : 269.75g/mol
- < Molecular formula : $C_{10}H_{22}NO_2Cl$
- ➢ Density : 1.29 ± 0.05 g/cm^3
- ➢ FT-IR(υ_{max}KBr) : 3455, 3077, 2906, 2361, 1966, 1888, 1649, 1566, 1448, 1416, 1202, 1188, 1138, 988, 860, 718, 601 cm^{-1}
- < ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 1.20 (t, J = 4.0 Hz, 3H, *methyl*), 3.08 (d, J = 7.2 Hz, 12H, *methyl*), 3.58 (m, J = 6.0 Hz, 2H, *methylene*), 4.13 (quartet, J = 22.4 Hz, 2H, *methine*), 4.70 (s, 1H, methylene), 7.733 (s, 1H, *ammonium*).



15

Synthesis of 2- amino carbonyl compound Mannich Base: (MB-01)

In a typical reaction, benzaldehyde (1 mmol), 3-methylaniline (1 mmol), cyclo- hexanone (1.1 mmol), and ionic liquids (0.20 g) as catalysts and solvent were stirred at room temperature (25 °C) in a round-bottomed flask. After a certain time the reaction mixture became viscous and solidified. At this stage the time was noted and the ionic liquid was separated from the reaction mixture by extraction with distilled water (5× 3 mL). The ionic liquid being soluble in water, so it comes in the water layer. The solid was separated by filtration and product was recrystallized from 98% ethanol and vacuum dried for 5 h.

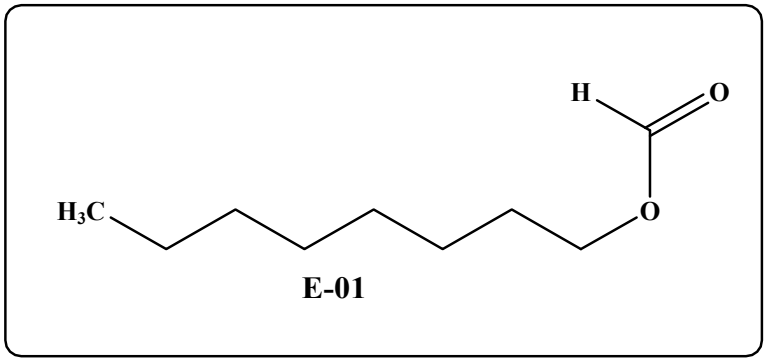
- Molecular weight : 294.84g/mol
- Molecular formula : $C_{20}H_{23}NO$
- Melting point : 136-138 ºC
- UV (λ_{max}, H_2O) : 261 nm
- FT-IR(υ_{max}KBr) : 3387.11, 3037.99, 2947.33, 2913.57, 2856, 2357,1701, 1595, 1540, 1486, 1456, 1308, 1207, 1120, 1027, 748, 705, 694 cm^{-1}
- ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 2.23 (s, 3H, *H10*), 2.84 (t, 1H, J = 6.8 Hz, *H7*), 2.48 (t, 2H, J = 3.6 Hz, *H6*), 1.90 (m, 4H, J = 5.6 Hz, *H3,4*), 1.74 (m, 2H, J = 5.6 Hz, *H5*), 6.44 (m, 3H, J = 7.2 Hz, *H11-13*), 6.98 (m, 1H, J = 7.2 Hz, *H9*), 7.30 (m, 5H, J = 7.2 Hz, *H14-18*),
- ^{13}C NMR (400 MHz, $CDCl_3$) ppm: 21, 23, 25, 27, 27.87, 28.77, 31.26, 41.76, 42.39, 56, 57, 58, 110, 115, 118, 127, 128, 138, 141, 146, 147, 211.29

Synthesis of octyl formate ester by esterification reaction: E-01

In the esterification reaction, octylalcohol 10 mmol and formic acid 10 mmol (equimolar amounts) and **K-IL: 05(13)** ionic liquids (0.20 mL) as catalysts were taken into a round bottomed flask at 100 °C for 24 hours. The progress of the reaction was monitored by TLC. At the end of the reaction, the mixture was left to cool. The reaction mixture was neutralized by the saturated solution of sodium bicarbonate. The pH was checked with pH paper, the indicated value was below 7, showing that not all the formic acid was neutralized. Solid sodium bicarbonate was added until the pH became weakly alkaline, indicated by the pH paper. The reaction mixture was filtered and washed with distilled H_2O. The sodium salt of

the formic acid was found in the water phase and the obtained ester was in the organic phase. The ionic liquid and unreacted formic acid were separated from the reaction mixture by extraction with distilled water (5× 3 mL). The ionic liquid is being soluble in water, so it came in the water layer. Ester was separated by solvent extraction and vacuum dried for 5 h.

- Molecular weight : 158.24 g/mol
- Molecular formula : $C_9H_{18}O_2$
- UV (λ_{max}, H_2O) : 238 nm
- FT-IR(υ_{max}KBr) : 3387.11, 3037.99, 2947.33, 2913.57, 2856, 2357,1701, 1595, 1540, 1486, 1308, 1207, 1120, 1027, 748, 705, 694 cm^{-1}
- ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 0.87 (t, J = 5.6 Hz, 3H, methyl), 1.26 (m, J = 6.4 Hz, 8H, methylene), 1.63 (m, J = 6.4 Hz, 2H, methylene), 3.59 (t, J = 6.8 Hz, 2H, methylene), 4.13 (t, J = 6.8 Hz, 2H, methylene), 8.02 (s, 1H, CHO).



E-01

RESULTS AND DISCUSSION

"SYNTHESIS AND CHARACTERIZATION OF PROTIC AMMONIUM BASED IONIC LIQUIDS"

N,N-Diisopropylethylammonium based ILs have been synthesized by the acid-base neutralization reaction of *N,N*-Diisopropylethylamine with carboxylic acid under mild condition. Yield percentage were (84-93) %. These ionic liquids were screened for antimicrobial toxicity and their applications in Mannich reaction and Esterification reaction were carry out. The synthesized ILs were characterized by using UV, FT-IR and NMR spectroscopy.

Characterization

Characterization of *N,N*-Diisopropylethylammonium trifluoroacetate, K-IL:05 (13):

A yellowish liquid was obtained with 95% yield, which was highly moisture sensitive. The structure of the compound was established by various spectral data.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig. 2.1, page 55) of the compound **13** showed the following peak:

- λ_{max} 254.0 nm : $\pi \rightarrow \pi^*$ Transition of C=O and CH_3 methyl group.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig. 2.2, page 56) of the compound **13** exhibited a number of bands, some of which were assigned as the follows at υ_{max} cm^{-1}:

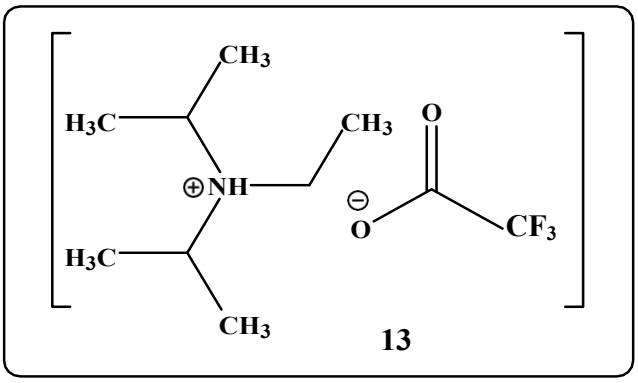
- 3435.35 : -NH stretching of quarternary ammonium.
- 2991.69 : -C–H stretching of aliphatic system.
- 1598.08 : C=O stretching of carboxylate group.
- 1135.15 : Revealed the stretching of –C-O bond.
- 1068.60 : C-F stretching.
- 777.34 : Aliphatic out of plane C-H bending.

iii) ^{1}H-NMR spectroscopy:

- The ^{1}H- NMR spectrum (Fig 2.3, page 57) of the compound **13** exhibited signals (in δ ppm) which were assigned as follows:

- 1.36 (t, J = 6.4 Hz, 3H, CH_3): three protons of methyl groups of amine.
- 1.42 (d, J = 7.6 Hz, 12H, CH_3) : twelve protons methyl groups.
- 3.55 (m, J = 2.8 Hz, 2H, CH) : two protons of methine .
- 3.1 (quartet, J = 4.0 Hz, 2H, CH_2): two protons of methylene.
- 10.55 (s, 1H, NH1) : one proton of ammonium for NH group.

The total twenty (20) proton atoms were obtained in the compound by ^1H NMR spectra. The spectral data of UV, FT-IR, and ^1H NMR data are compatible with the structure of this compound shown as below:



13

K-IL: 05 (13)

Characterization of *N,N*-Diisopropylammonium-2-bromopropionate K- IL: 06 (14):

A yellowish liquid was obtained with 91% yield, which was moisture sensitive. The structure of the compound was established by various spectral data.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig 2.5, page 59) of the compound **14** showed the following peak:

- λ_{max} 252.0 nm : $\pi \rightarrow \pi^*$ Transition of C=O and CH_3 bonded group.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig 2.6, page 60) of the compound **14** exhibited a number of bands, some of which were assigned as the follows at υ_{max} cm^{-1}:

- 3440.16 : -NH stretching of ammonium cation.
- 2983.98 : aliphatic -CH_3 stretching
- 1721.53 : C=O stretching of carboxylate.
- 1217.12 : Revealed the stretching of –C-O bond.

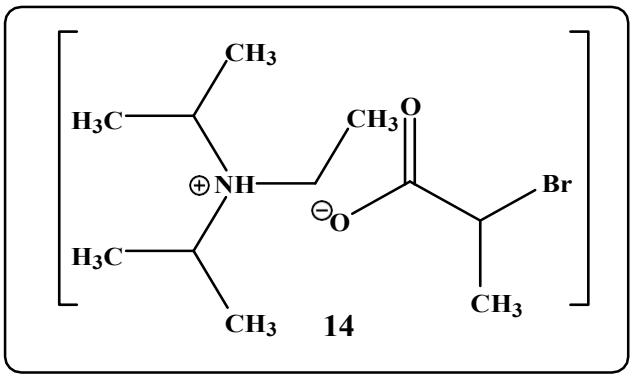
- 633.64 :C-Br stretching.

iii) ^{1}H-NMR spectroscopy:

The ^{1}H- NMR spectrum (Fig 2.7, page 61) of the compound **14** exhibited signals (in δ ppm) which were assigned as follows:

- 1.08 (t, J = 3.6 Hz, 3H, C*H*$_3$) : three protons of cataonic methyl groups.
- 1.26 (d, J = 6.8 Hz, 12H, CH_3): twelve protons of cataonic methyl group.
- 1.43 (d, J = 5.6 Hz, 3H, CH_3) : three protons of anaonic methyl group.
- 3.12 (m, J = 3.2 Hz, 2H, CH_2) : two protons of ammonium methelene.
- 3.63 (m, J = 6.4 Hz, 2H, CH) : two protons of cataonic methine group.
- 4.30 (quartet, J = 7.2 Hz, 1H, CH) : one proton of anionic methine group.
- 5.01 (s, 1H, N*H1*) : one proton of ammonium for NH group.

The total twenty-four (24) proton atoms were obtained in the compound by ^{1}H NMR spectra. The spectral data of UV, FT-IR, and ^{1}H NMR data are compatible with the structure of this compound shown as below:



14

K-IL: 06 (14)

Characterization of *N,N*-Diisopropylethylammonium-2-chloroacetate, K-IL: 07 (15):

A colorless liquid was obtained with 90% yield, which was moisture sensitive. The structure of the compound was established by various spectral data.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig 2.9, page 63) of the compound **15** showed the following peak:

- λ_{max} 284.0 nm : $\pi \rightarrow \pi^*$ Transition of C=O, chromophore methyl group.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig 2.10, page 64) of the compound **15** exhibited a number of bands, some of which were assigned as the follows at υ_{max} cm^{-1}:

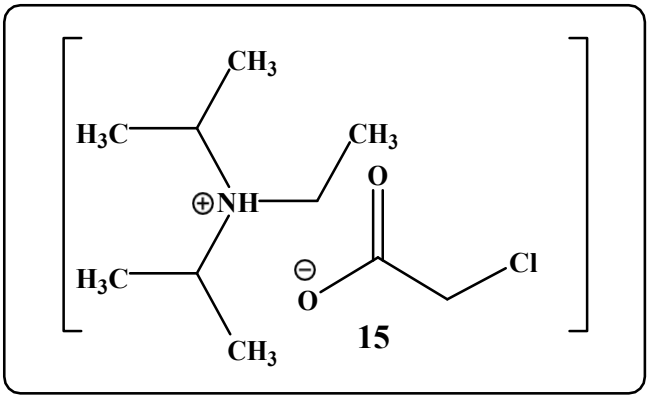
- 3455 : -NH stretching of cataonic group.
- 2959 : aliphatic N-CH_3 stretching .
- 1649 : C=O stretching of carboxylate ion.
- 3096, 2986 : -C–H stretching.
- 1134 : Revealed –C-O bond.
- 1188 : Revealed the stretching of –C-O bond.
- 786.02 : C-Cl bending of carboxylate anion .

iii) ^{1}H-NMR spectroscopy:

The ^{1}H- NMR spectrum (Fig 2.11, page 65) of the compound **15** exhibited signals (in δ ppm) which were assigned as follows:

- 1.20 (t, J = 4.0, 3H, CH_3) : three protons of amine methyl groups.
- 3.08 (d, J = 7.2 Hz, 12H, CH_3) : twelve protons of ammonium of methyl.
- 3.58 (m, J = 6.0 Hz, 2H, CH_2) : two protons of ammonium of methylene.
- 4.13 (quartet, J = 22.4 Hz, 2H, CH) : two protons of cataonic methane group.
- 4.70 (s, 2H, CH_2) : two protons of anionic –CH_2 group.
- 7.73 (s, 1H, NH1) : one proton of ammonium –NH group.

The total twenty-two (22) proton atoms were obtained in the compound by ^{1}H NMR spectra. The spectral data of UV, FT-IR, and ^{1}H NMR data are compatible with the structure of this compound shown as below:



K-IL:07 (15)

Characterization of Octylformate ester, E-01:

A colorless liquid octylformate ester was obtained with 81.5% yield and density 1.08 g/cm^3 which was non moisture sensitive. The structure of the compound was established by various spectral data.

i) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig 2.13, page 67) of the compound **E-01** exhibited a number of bands, some of which were assigned as the follows at υ_{max} cm^{-1}:

- 2931.90 : C-H stretch (alkyl).
- 1732.13 : Saturated ester C=O stretch.
- 1054.13 : C-O stretches.
- 748, 628 : Aliphatic out of plane C-H bending.

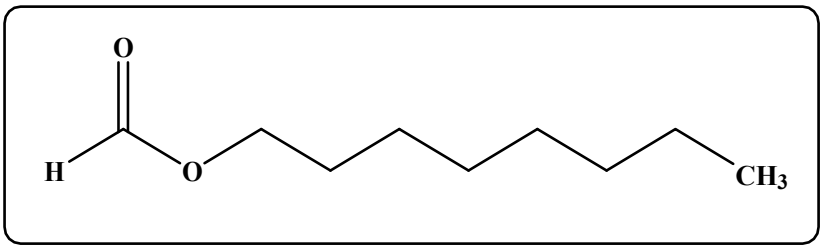
ii) ^{1}H-NMR spectroscopy:

The ^{1}H- NMR spectrum (Fig 2.14, page 68) of the compound **E-01** exhibited signals (in δ ppm) which were assigned as follows:

- 0.87 (t, 3H, J = 5.6Hz, CH_3) : three protons of octyl methyl functional group.
- 1.26 (m, 8H, J = 6.4 Hz, CH_2) : eight protons of methylene of alkyl group.
- 1.63 (m, 2H, J = 6.4 Hz, CH_2) : two protons of methylene group.
- 3.59 (t, 2H, J = 6.8 Hz, CH_2) : triplet, two protons of methylene.
- 4.13 (t, 2H, J = 6.8 Hz, CH_2) : two protoms of methelene functional group.
- 8.02 (s, 1H, CHO) : one proton of formic acid -CH.

The total eighteen (18) proton atoms were obtained in the compound by ^{1}H NMR spectra.

The spectral data of UV, FT-IR, and ^{1}H NMR data are compatible with the structure of this compound shown as below:



Octylformate ester, E-01

Characterization of 2-amino carbonyl compound, (MB-01):

A white solid was obtained with 97% yield, mp 136-138 °C, which was not moisture sensitive. The structure of the compound was established by various spectral data.

i) UV-visible spectroscopy:

The UV-visible spectrum (Fig 2.16, page 70) of the compound **MB-01** showed the following peak:

- λ_{max} 261.0 nm : $\pi \rightarrow \pi^*$ Transition of C=C aromatic system.

ii) FT-infrared spectroscopy:

The FT-IR (KBr) spectrum (Fig 2.17, page71) of the compound **MB-01** exhibited a number of bands, some of which were assigned as the follows at υ_{max} cm^{-1}:

- 3387.11 : one broad peak for –NH bond stretching.
- 3037.99 : -C–H bond stretching of aromatic system.
- 2947, 2913 : bond stretching of cyclic $–CH_2$ & aliphatic –CH group.
- 1701 : cyclic carbonyl –CO- bond stretching.
- 1595 : C=C double bond stretch of aromatic ring.
- 1456, 1340 : medium to strong absorptions of aromatic ring.
- 1207 : $-CH_2$ out of plane bending of cyclic methelene.
- 1120 : revealed the stretching of –C-O bond.
- 748, 705 : Aromatic out of plane C-H bending.

iii) ^{1}H-NMR spectroscopy:

The ^{1}H- NMR spectrum (Fig 2.18, page 72) of the compound **MB-01** exhibited signals (in δ ppm) which were assigned as follows:

- 1.90 (m, 4H, J = 5.6 Hz, C3,4) : cyclic four protons of C-3 and C-4 methelene group.
- 1.74 (m, 2H, J = 5.6 Hz, C-5) : methelene two protons of C-5 moiety.
- 2.23 (s, 3H, C-10) : three C-10 methyl protons.
- 2.48 (t, 2H, J = 3.6 Hz, C-6) : two protons of C-6 in cyclohexanone ring.
- 2.84 (t, 1H, J = 6.8 Hz, C-7) : one aliphatic C-7 chiral proton.
- 4.64 (d, 1H, J = 7.2 Hz, C-8) : one proton of secondary –NH amine.
- 4.84 (d, 1H, J = 4.4 Hz, C-2) : chiral proton of C-2.
- 6.44 (m, 3H, J = 7.2 Hz, C11-13) : three protons of aromatic C-11,12,13.
- 6.98 (m, 1H, J = 7.2 Hz, C9) : -CH proton of C-9 in aromatic system.
- 7.30 (m, 5H, J = 7.2 Hz, C14-18) : five protons of phenyl ring C-(14-18).

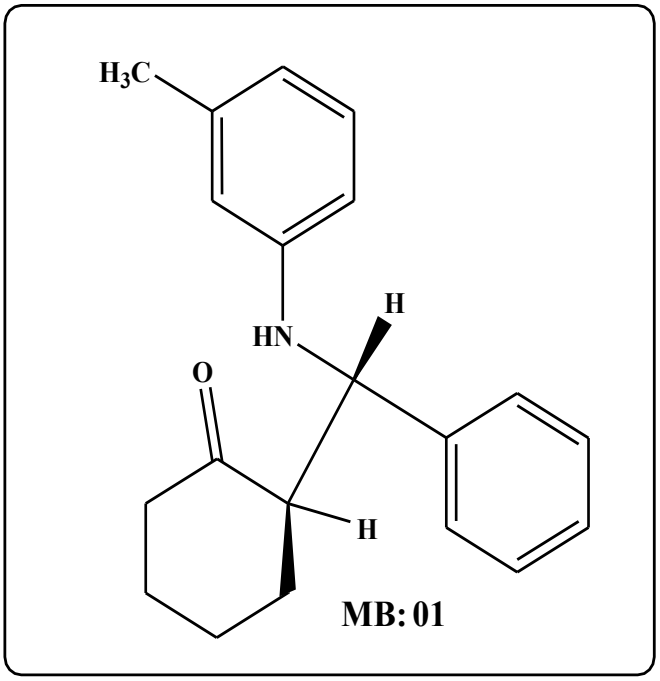
iv) ^{13}C-NMR spectroscopy:

The ^{13}C- NMR spectrum (Fig 2.21, page 75) of the compound **MB-01** showed several signals which were assigned as follows:

- 21.01 : one saturated aliphatic C-10 carbon.
- 23, 25, 27, 27.87, 28.77 : five cyclic saturated carbons of C-(2-6).
- 31.26 : one chiral carbon C-7, which is saturated.
- 43, 56, 58, 110, 115, 118 : six unsaturated aromatic ring carbons, C-(14-18).
- 127, 128, 138, 141, 146, 147 : six carbons of aromatic system C-(8-13).
- 211.29 : one C=O carbon C-1, unsaturated in cyclohexanone.

The total twenty-three (23) proton atoms and twenty (20) carbons were obtained in the compound by ^{1}H NMR spectra.

The spectral data of UV, FT-IR, ^{1}H NMR, ^{13}C NMR data are compatible with the structure of this compound shown as below:



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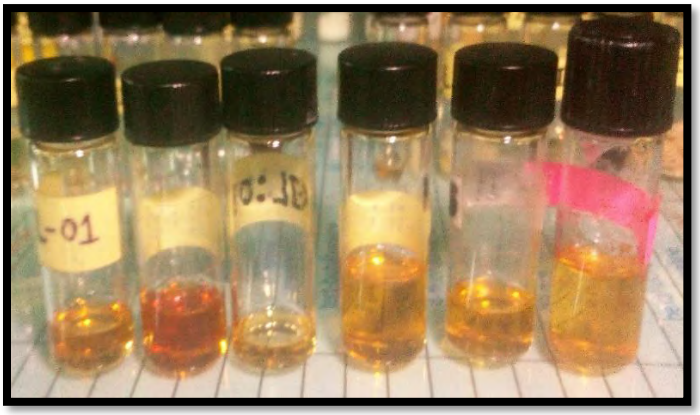


Synthesized protic *N, N*-Diisopropylethylammonium based ionic liquids.

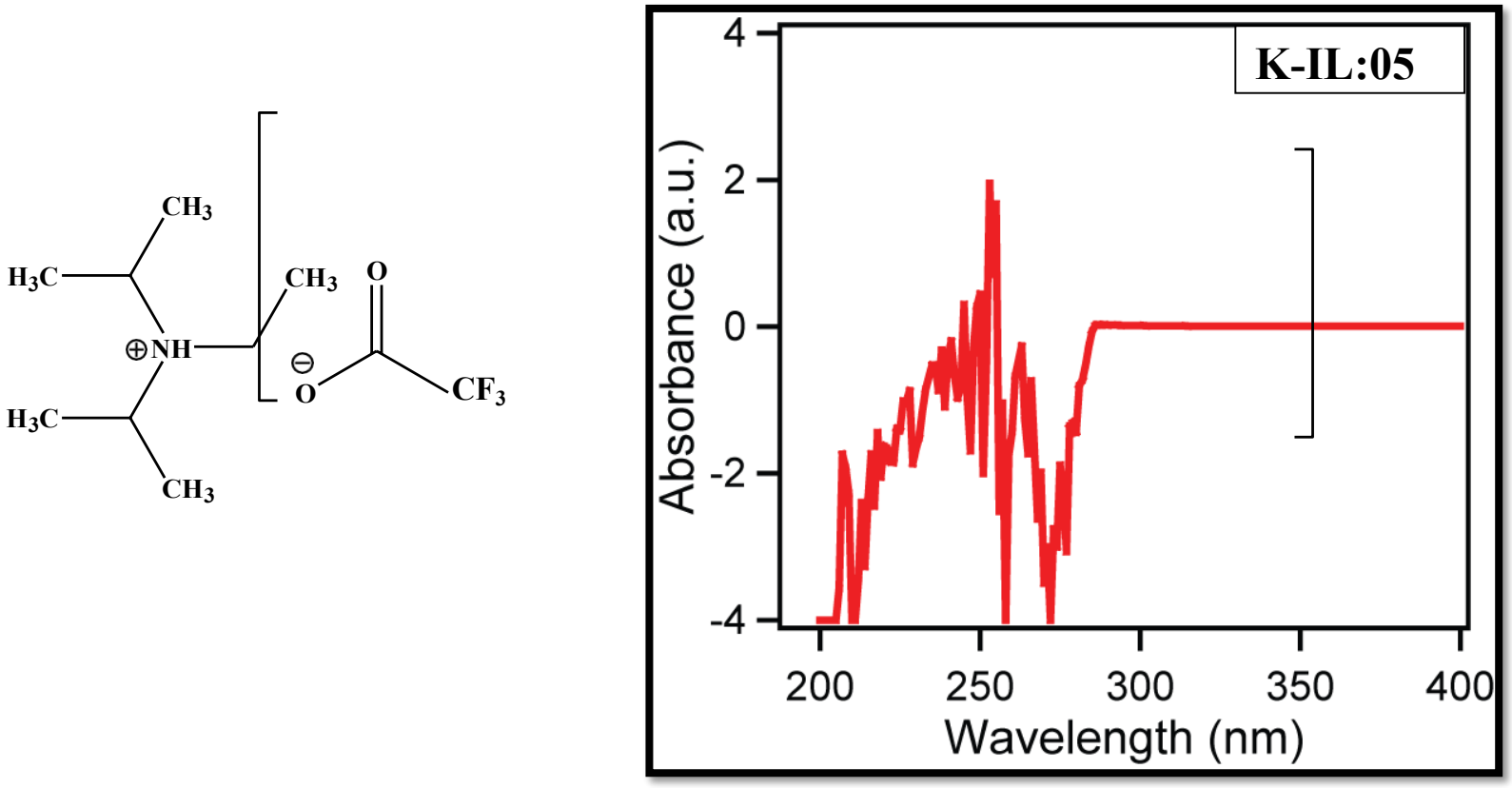


Fig 2.1: UV-VIS spectrum of synthesized ionic liquid of K-IL: 05 (256 nm)

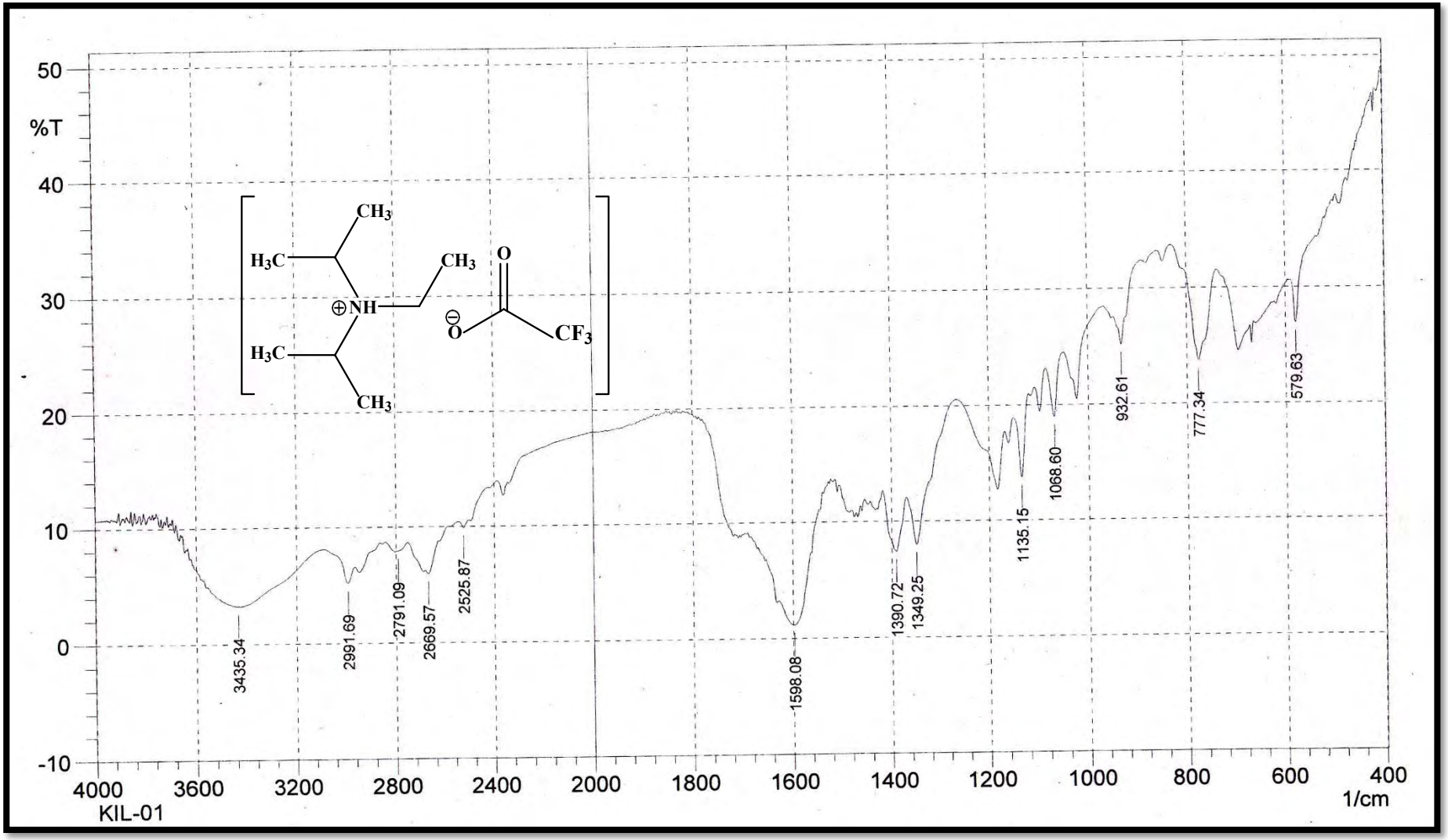


Fig 2.2: FT-IR spectrum of synthesized ionic liquid of K-IL: 05 (13)

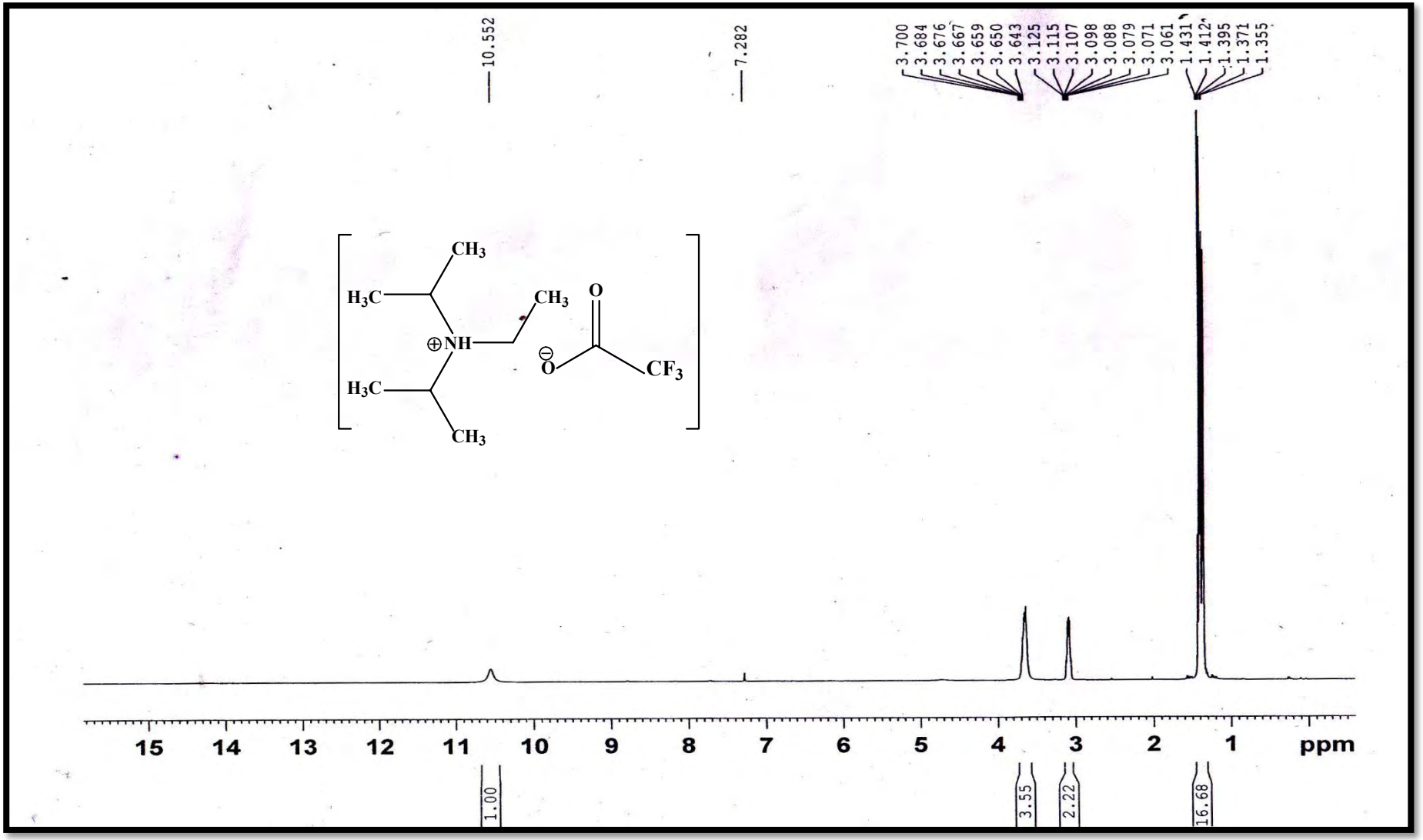


Fig 2.3: ^{1}H-NMR spectrum of synthesized ionic liquid of K-IL: 05 (13)

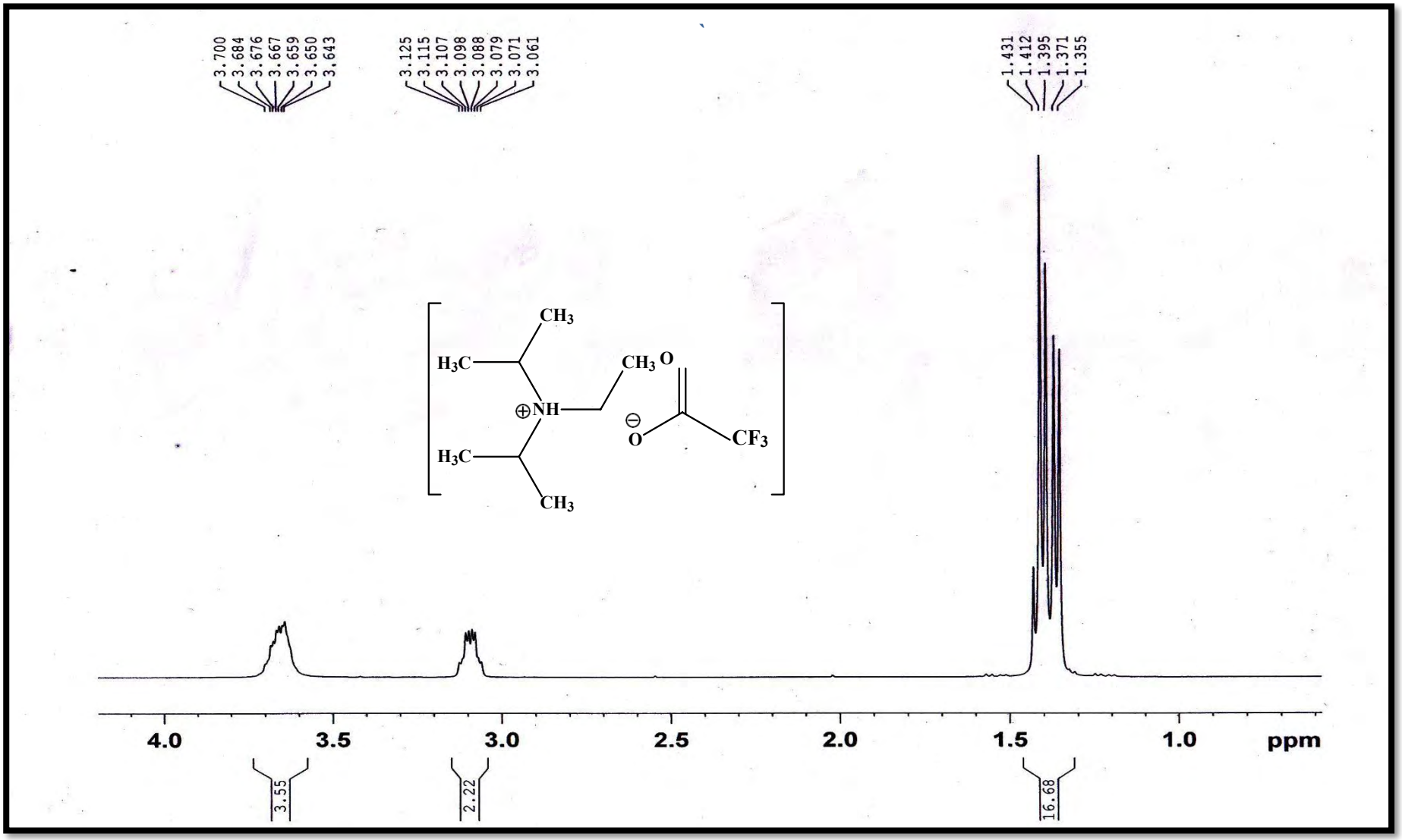


Fig 2.4: ^{1}H-NMR spectrum of synthesized ionic liquid of K-IL: 05 (13)

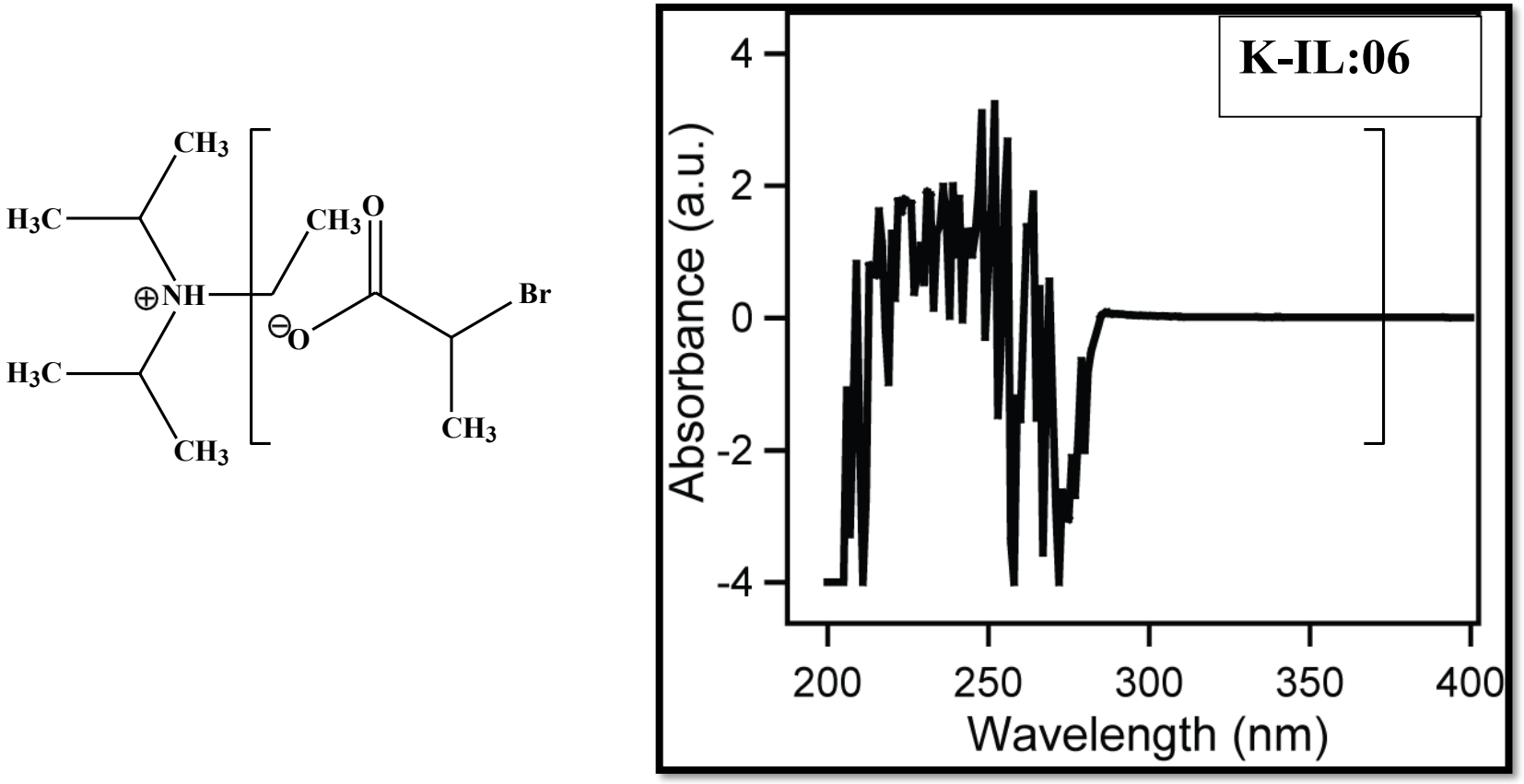


Fig 2.5: UV-VIS spectrum of synthesized ionic liquid of K-IL: 06 (254 nm)

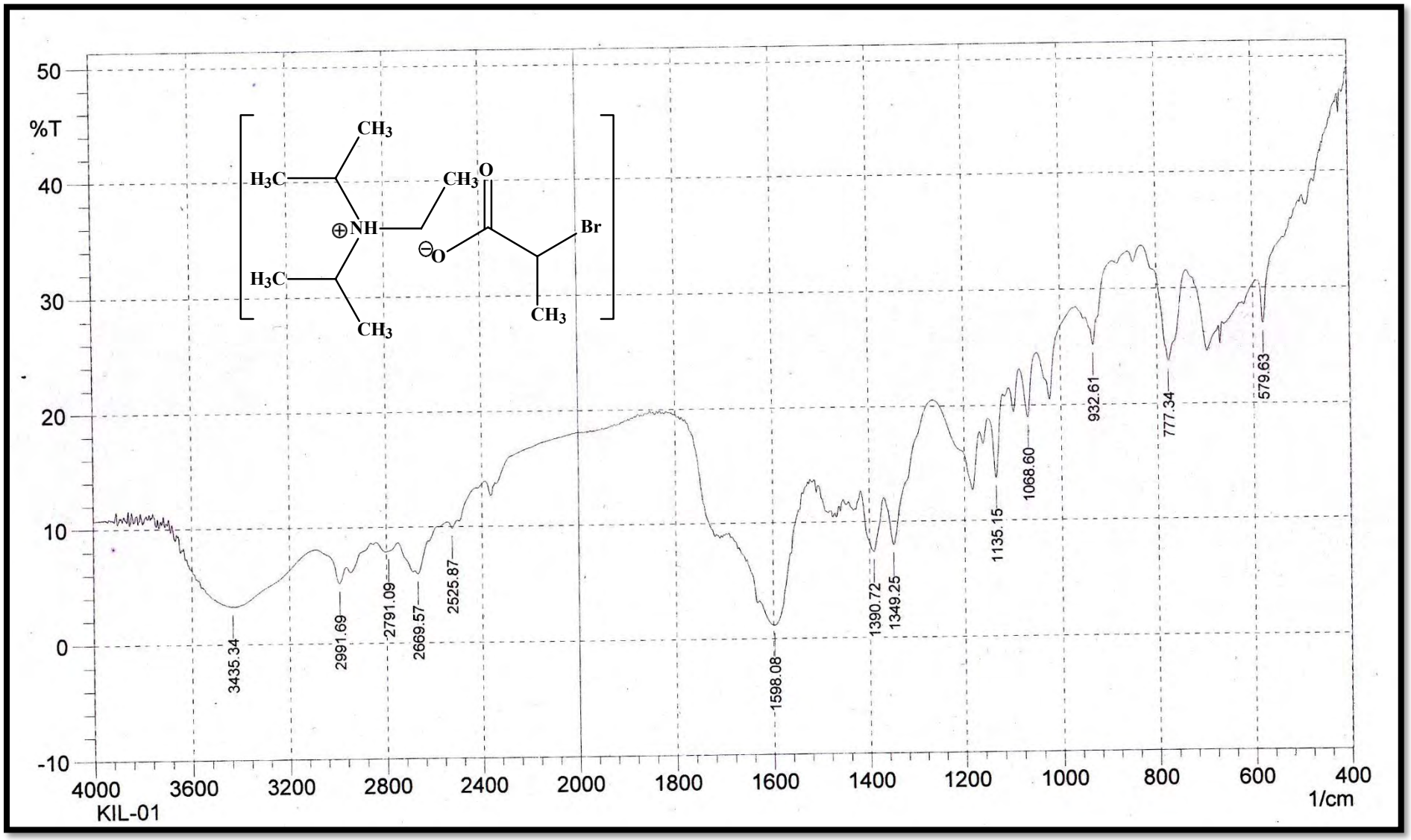


Fig 2.6: FT-IR spectrum of synthesized ionic liquid of K-IL: 06 (14)

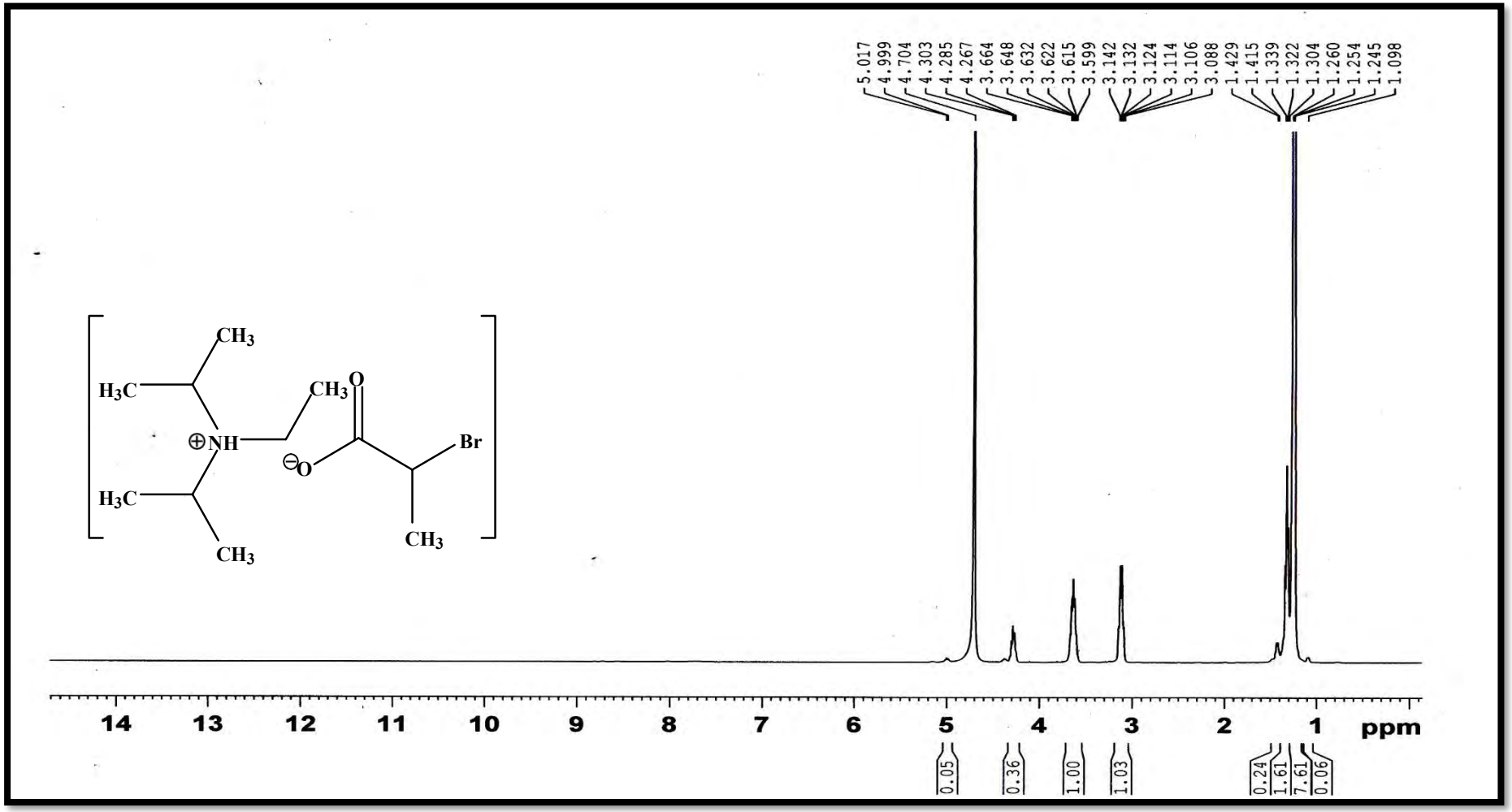


Fig 2.7: ^{1}H-NMR spectrum of synthesized ionic liquid of K-IL: 06 (14)

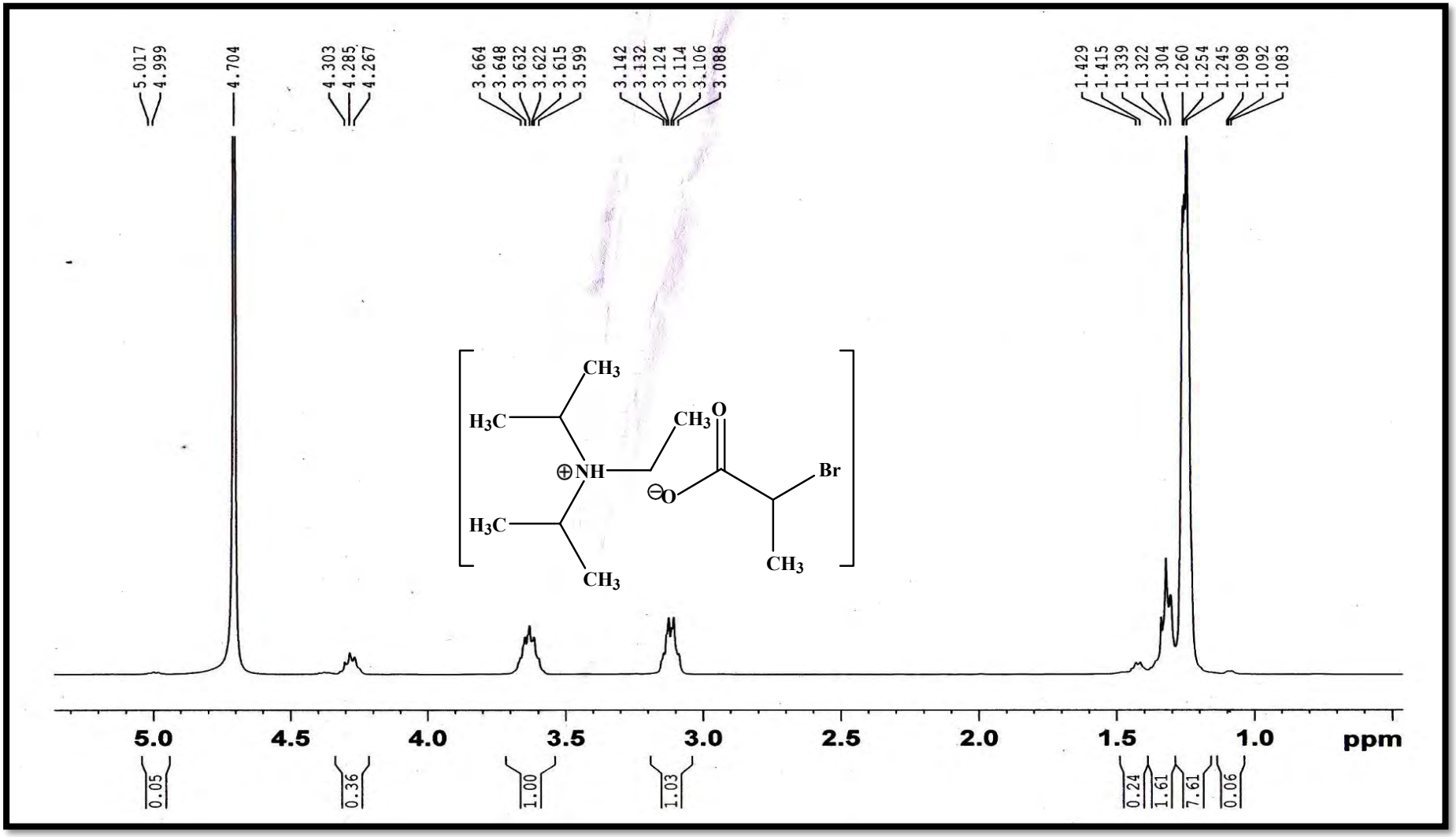
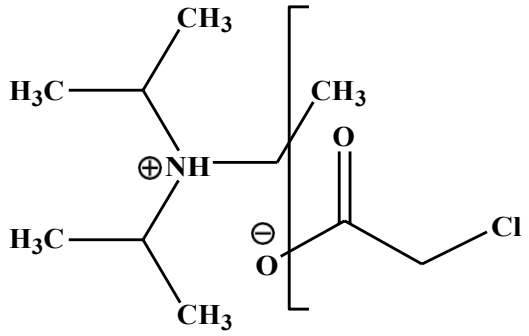


Fig 2.8: ^{1}H-NMR spectrum of synthesized ionic liquid of K-IL: 06 (14)



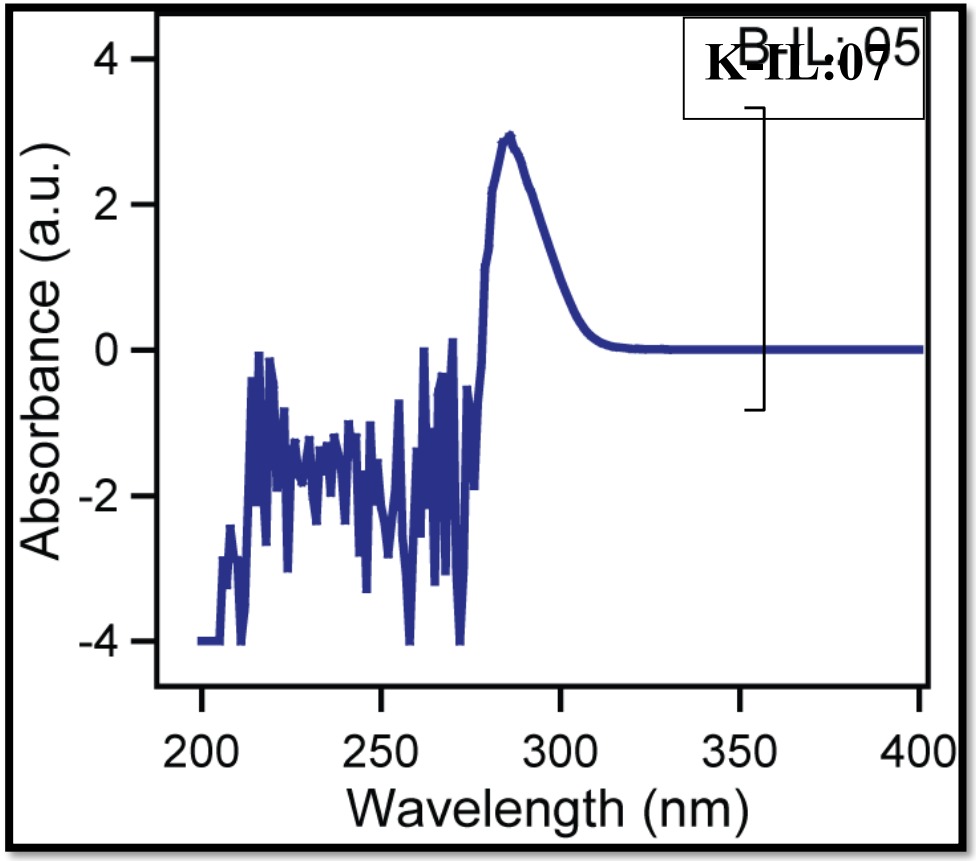


Fig 2.9: UV-VIS spectrum of synthesized ionic liquid of K-IL: 07(15) (283 nm)

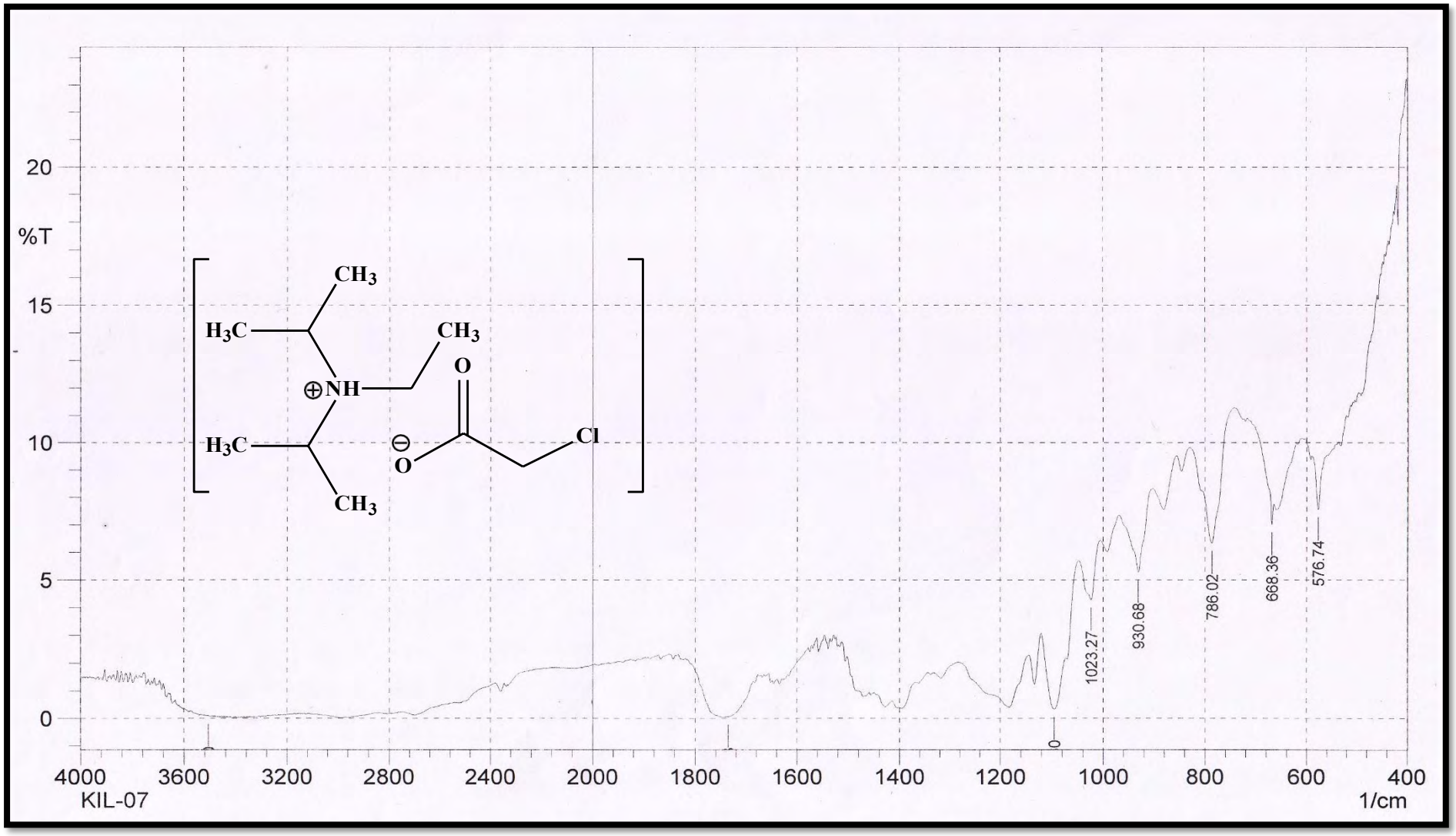


Fig 2.10: FT-IR spectrum of synthesized ionic liquid of K-IL: 07 (15)

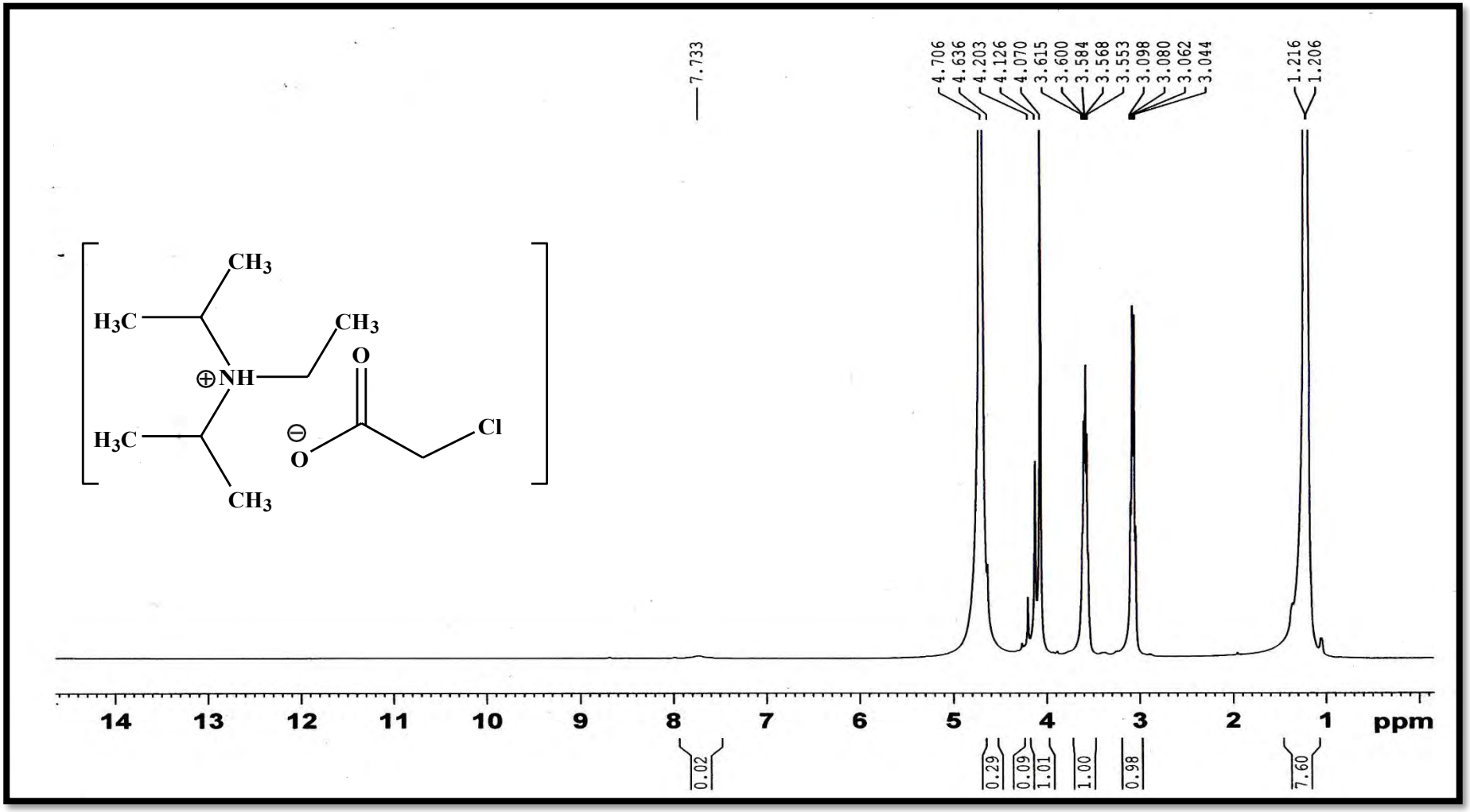


Fig 2.11: ^{1}H-NMR spectrum of synthesized ionic liquid of K-IL: 07 (15)

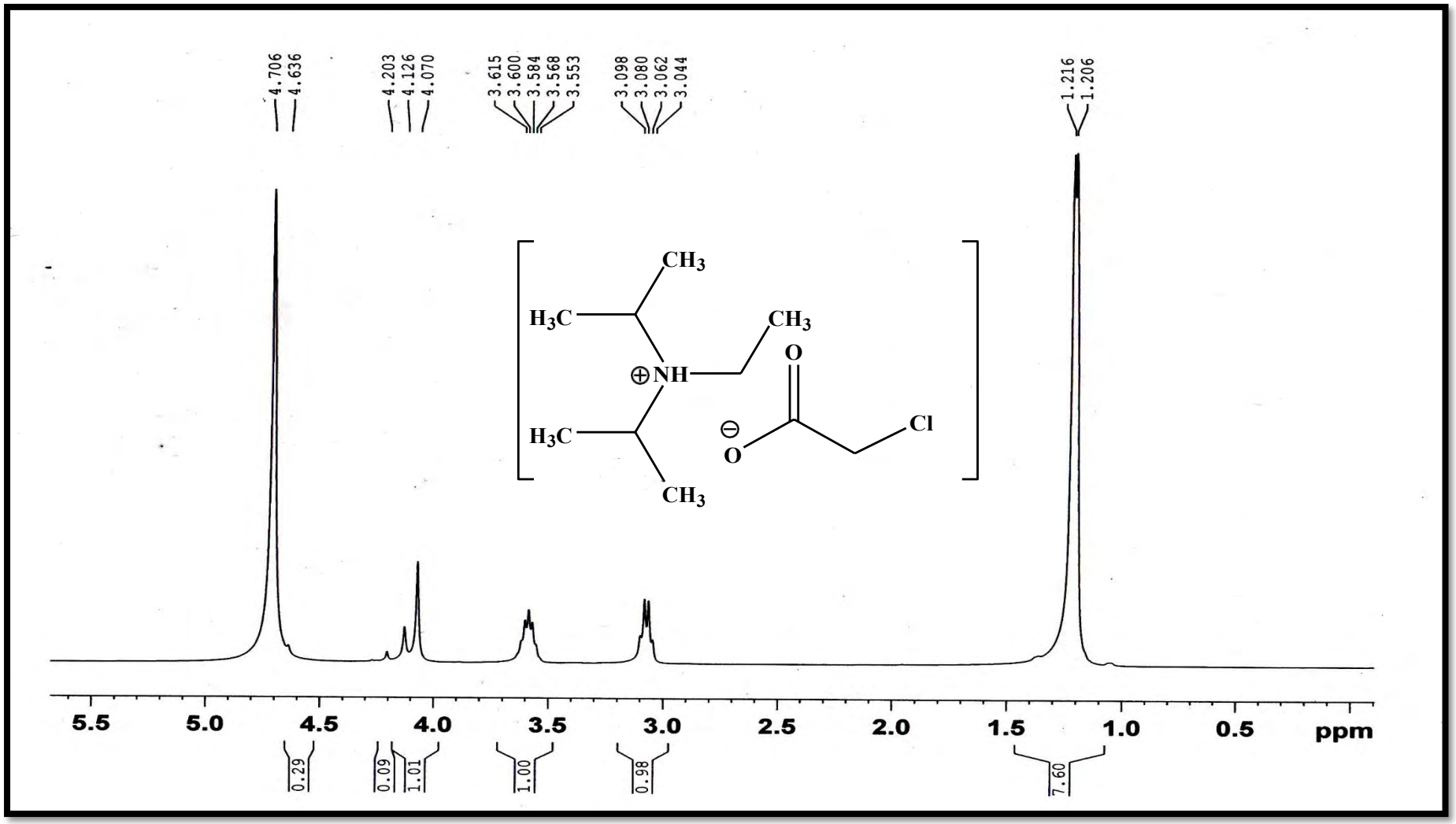


Fig 2.12: ^{1}H-NMR spectrum of synthesized ionic liquid of K-IL: 07 (15)

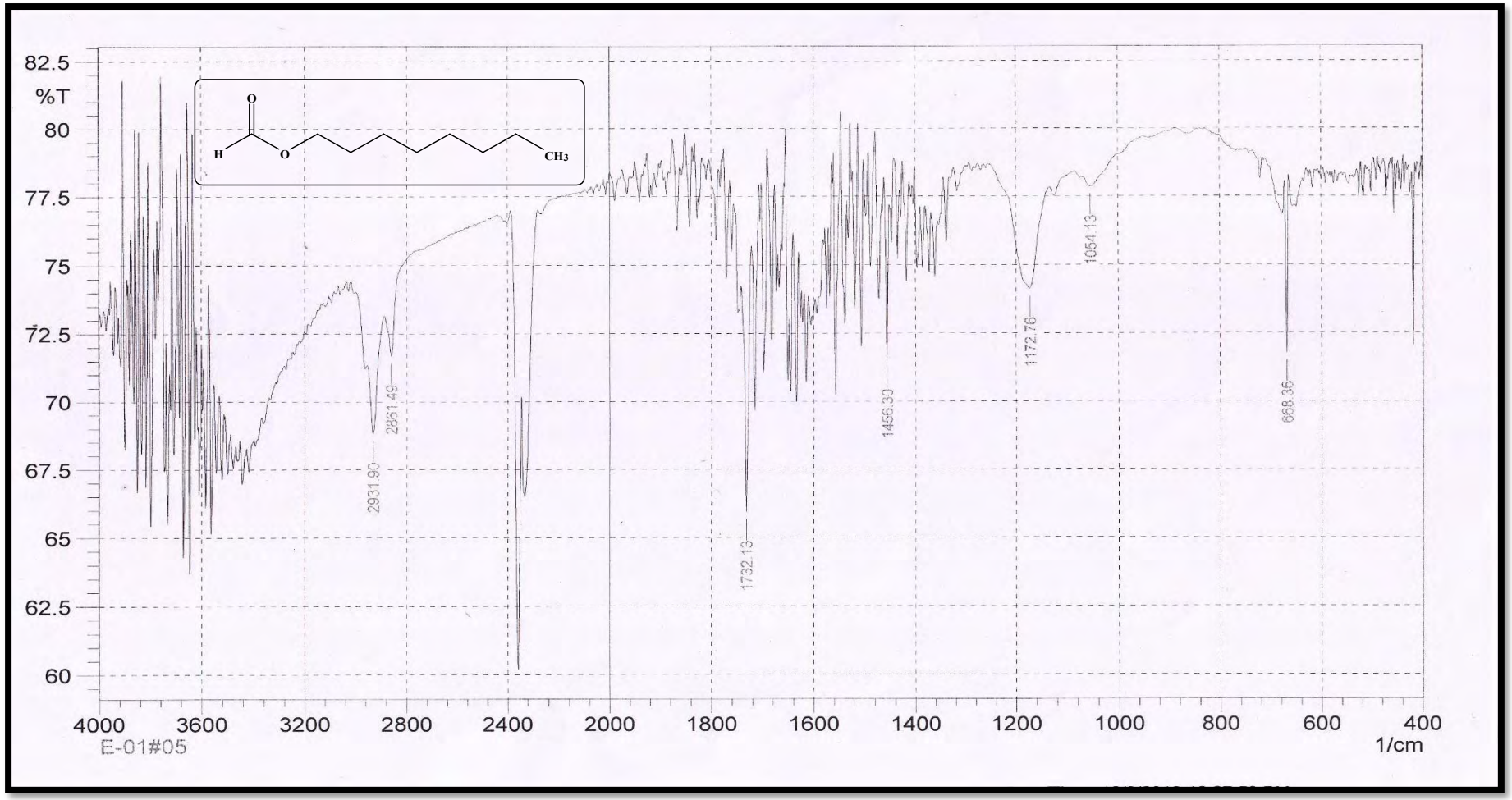


Fig 2.13: FT-IR spectrum of synthesized octylformate ester of E:01

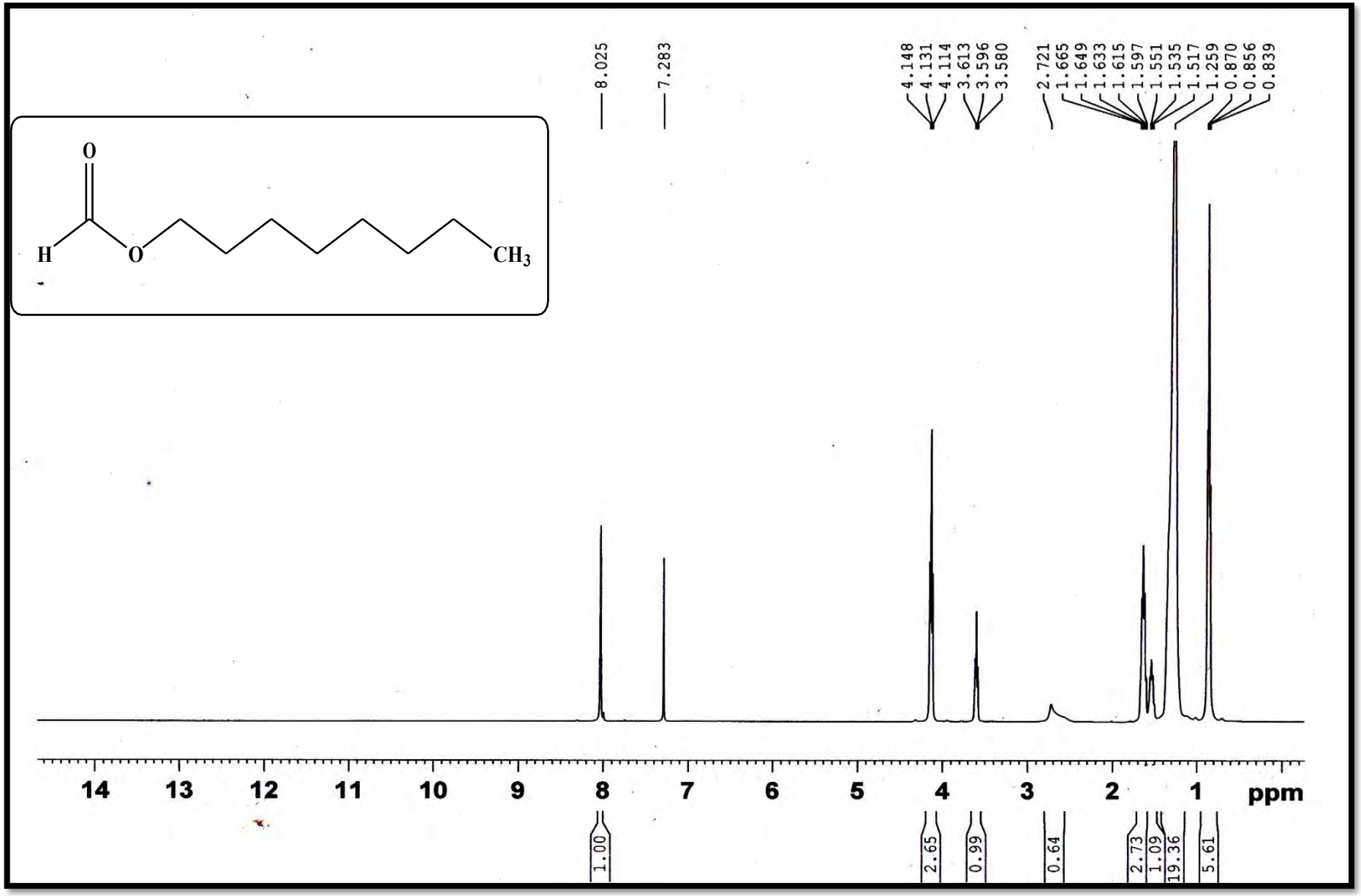


Fig 2.14: ^{1}H-NMR spectrum of synthesized octylformate ester of E:01

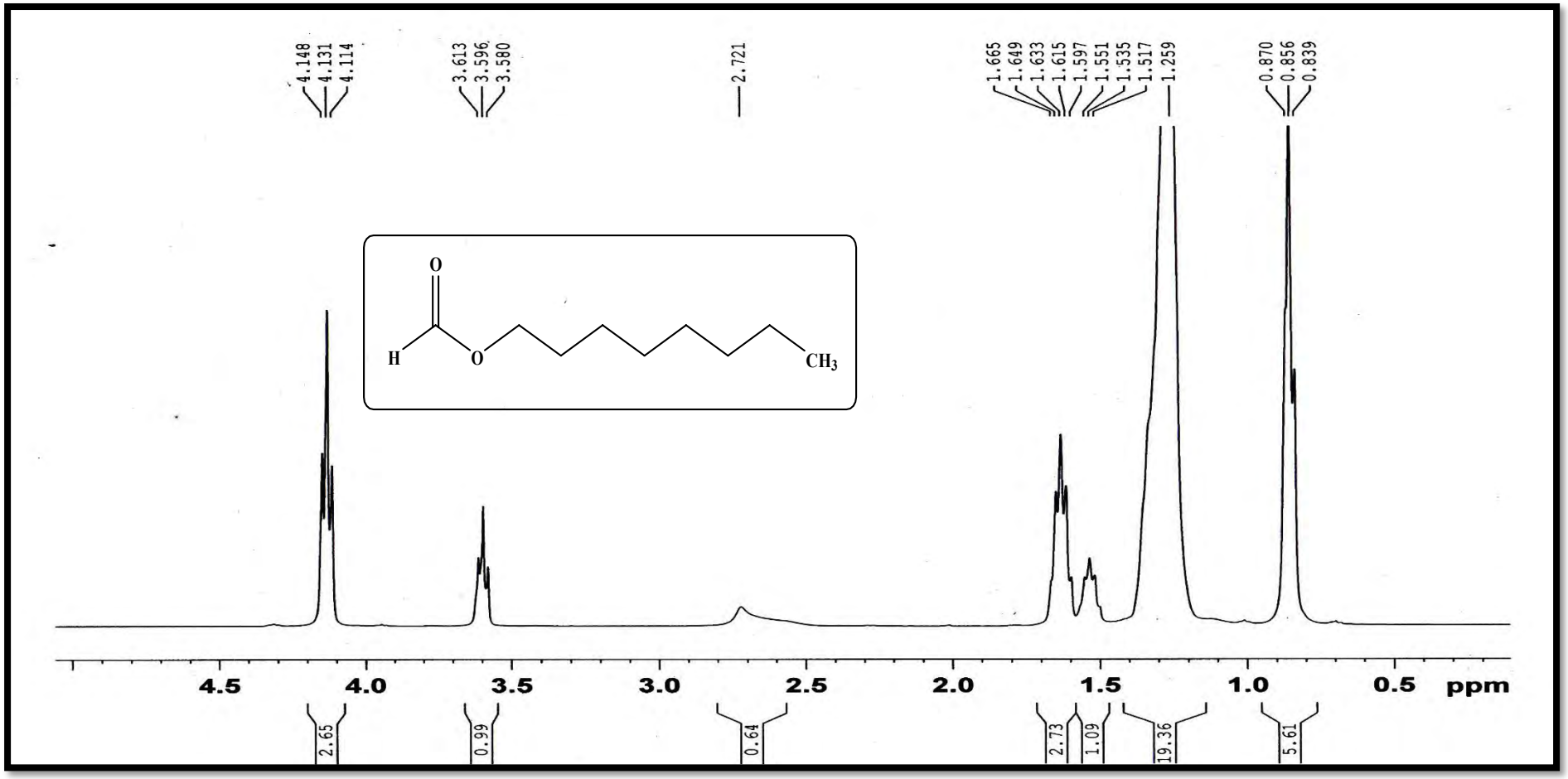
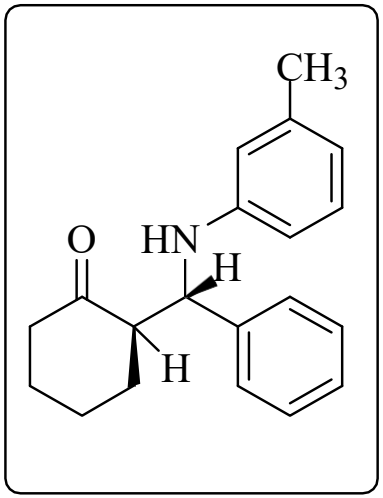


Fig 2.15: ^{1}H-NMR spectrum of synthesized octylformate ester of E:01



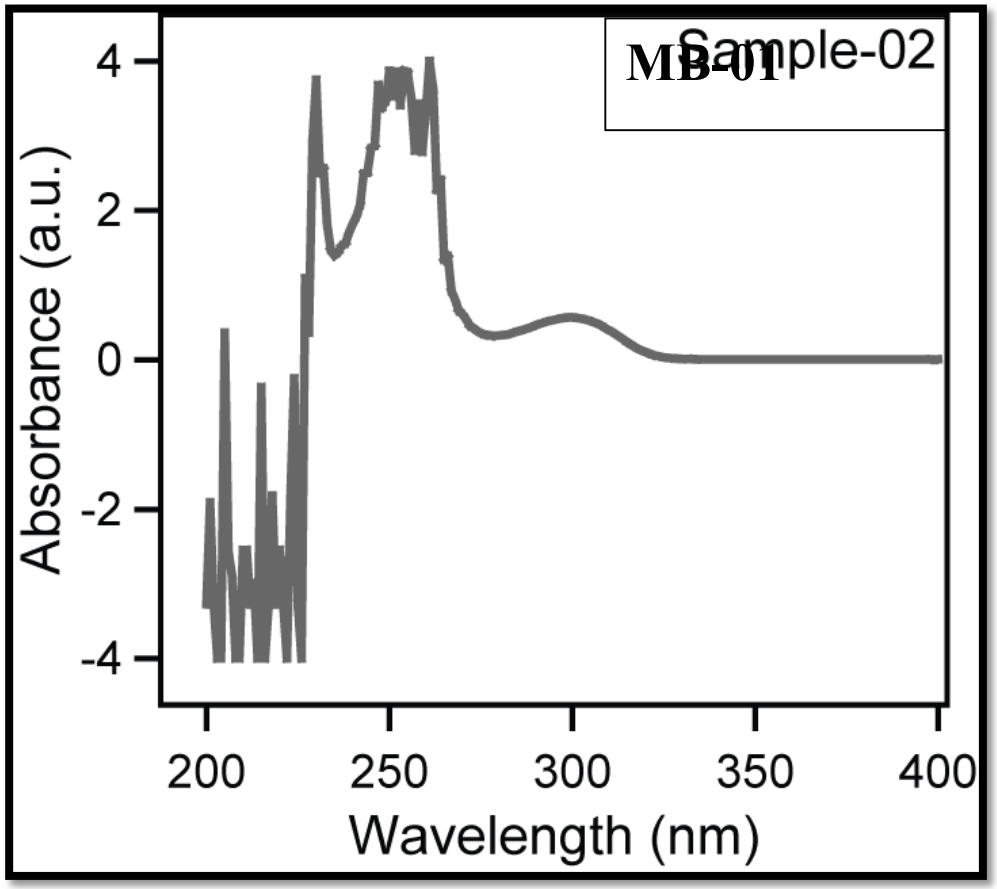


Fig 2.16: UV-VIS spectrum of synthesized Mannich compound of MB-01 (261 nm)

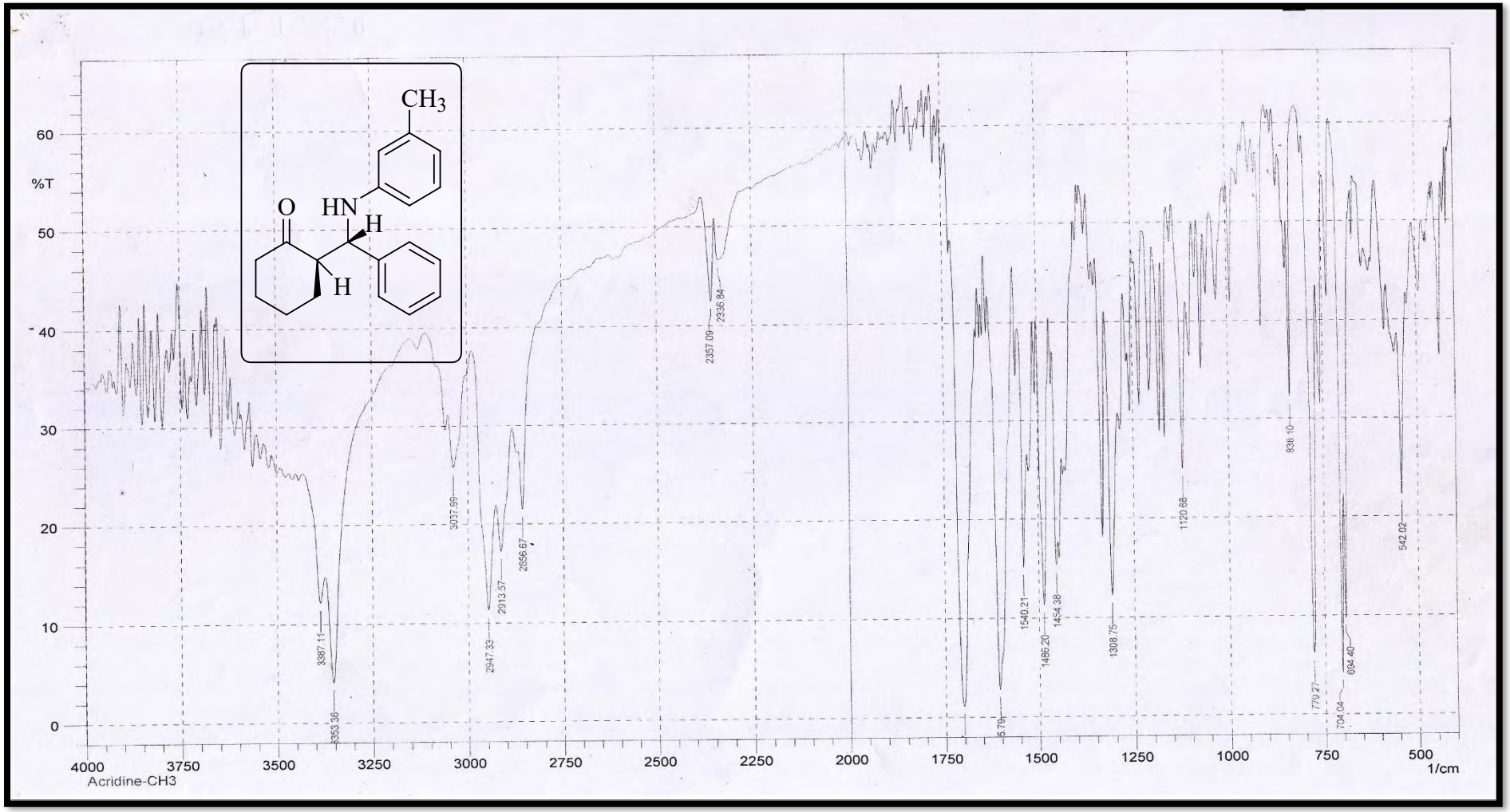


Fig 2.17: FT-IR spectrum of synthesized Mannich Compound (MB:01)

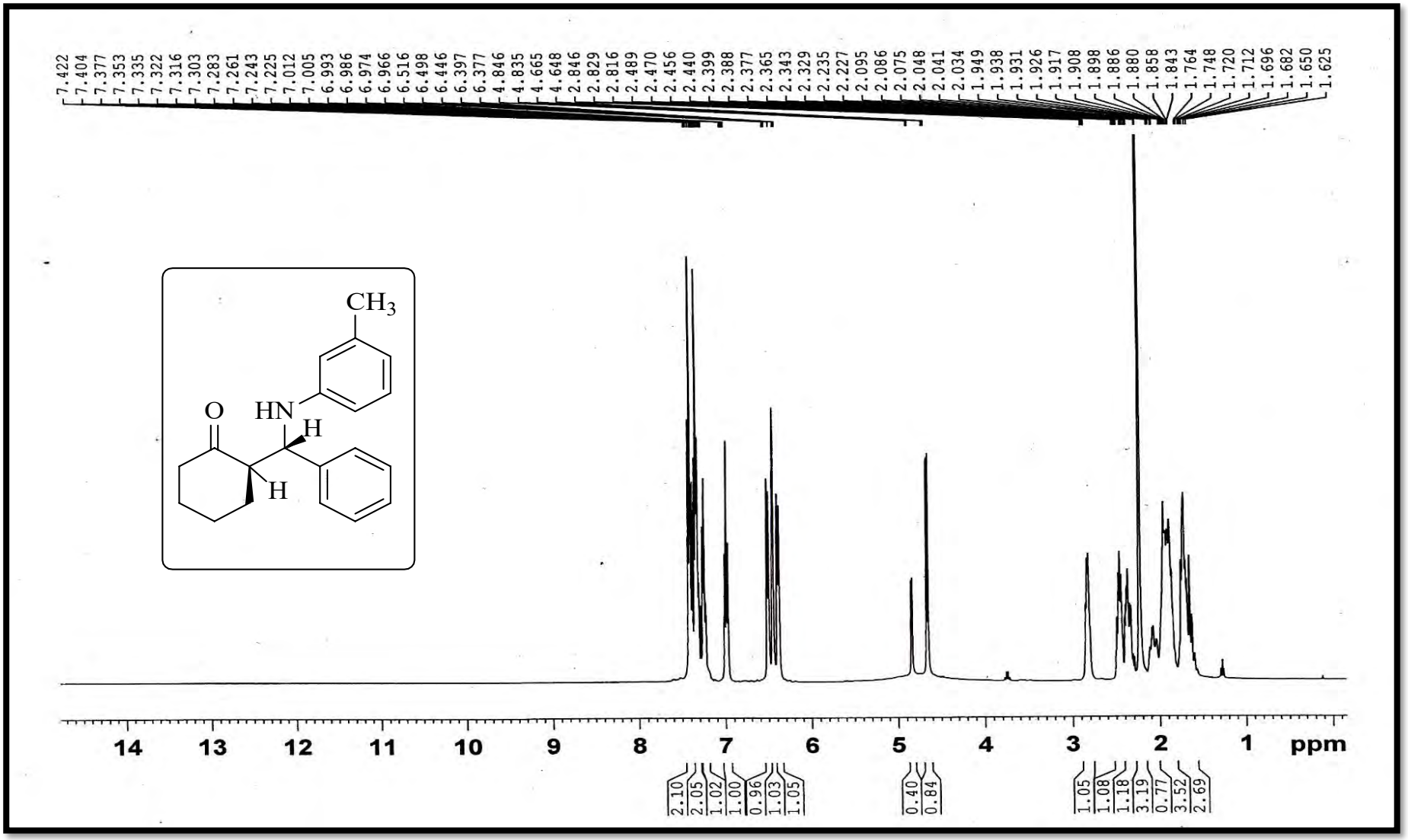


Fig 2.18: ^{1}H-NMR spectrum of synthesized Mannich compound of MB-01

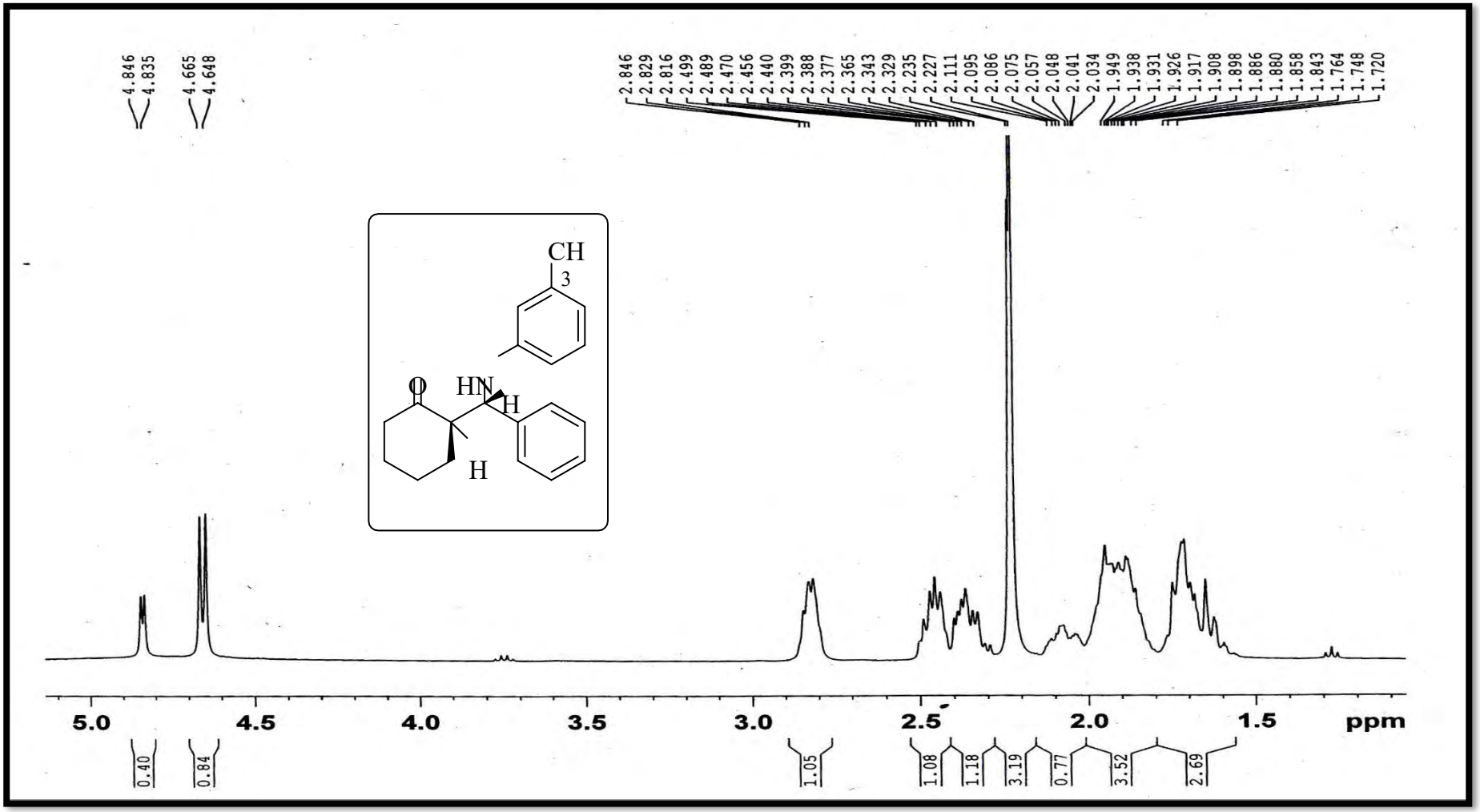


Fig 2.19: ^{1}H-NMR spectrum of synthesized Mannich compound of MB-01

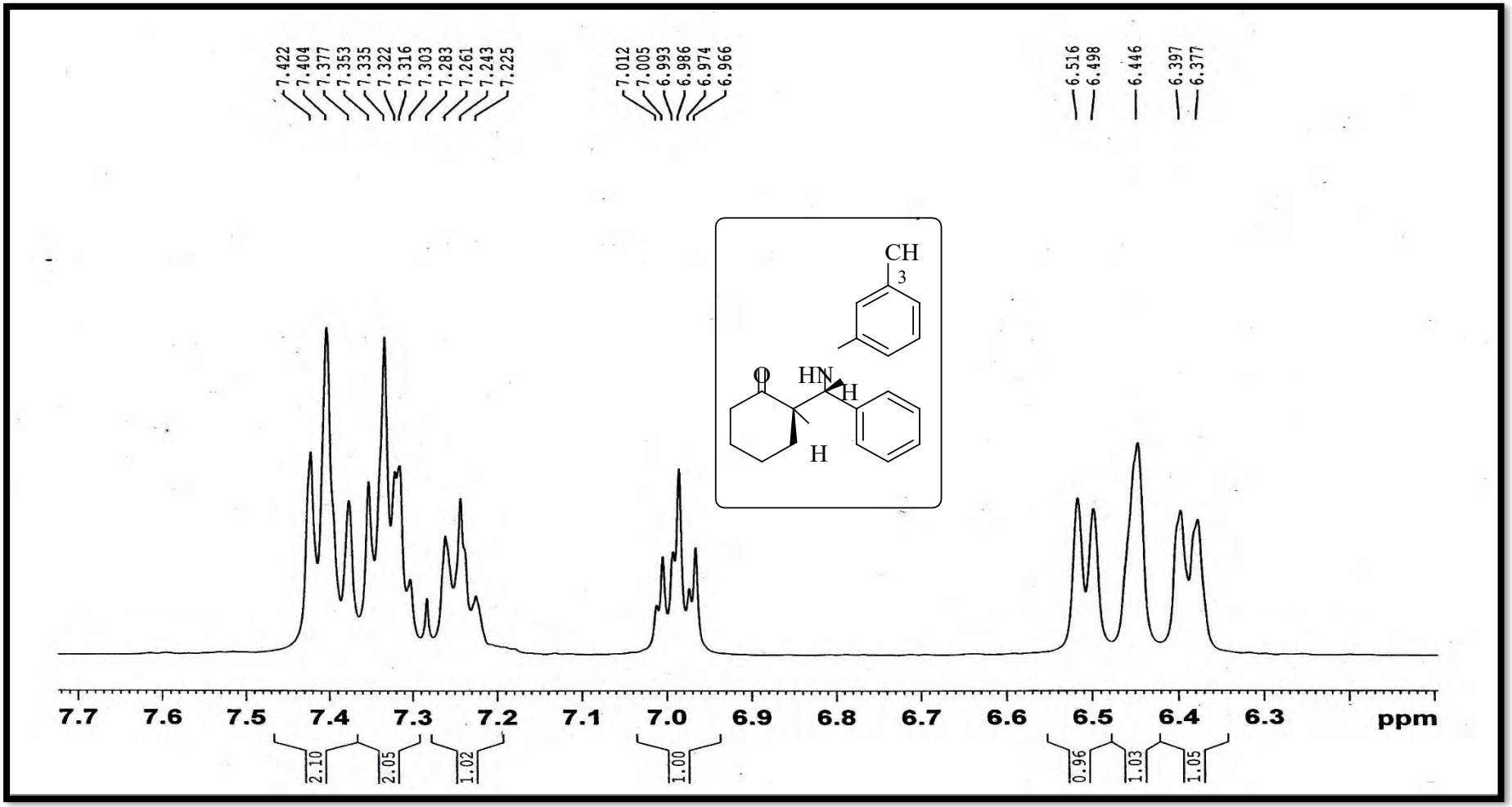


Fig 2.20: ^{1}H-NMR spectrum of synthesized Mannich compound of MB-01

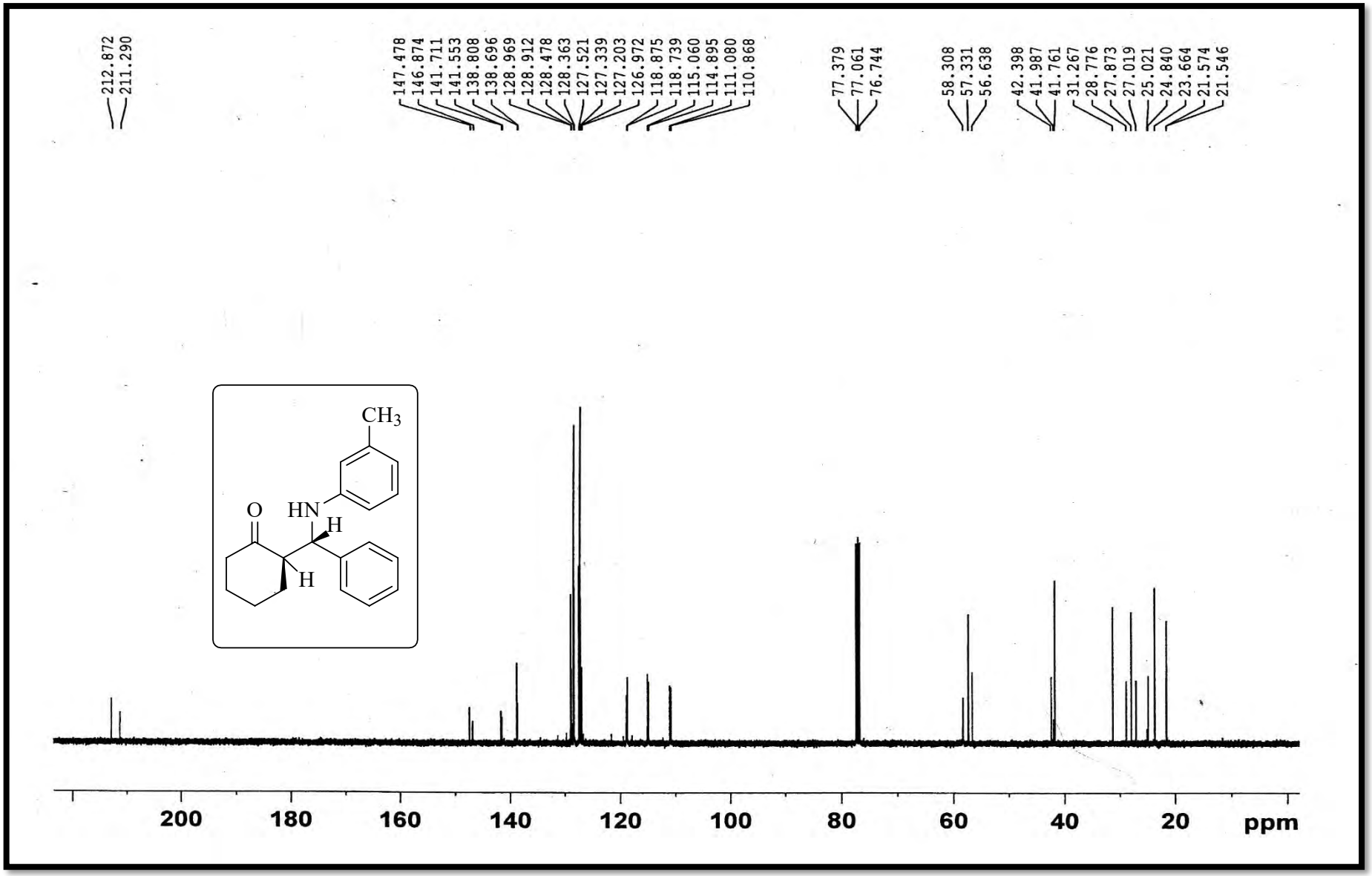


Fig 2.21: ^{13}C-NMR spectrum of synthesized Mannich compound of MB-01

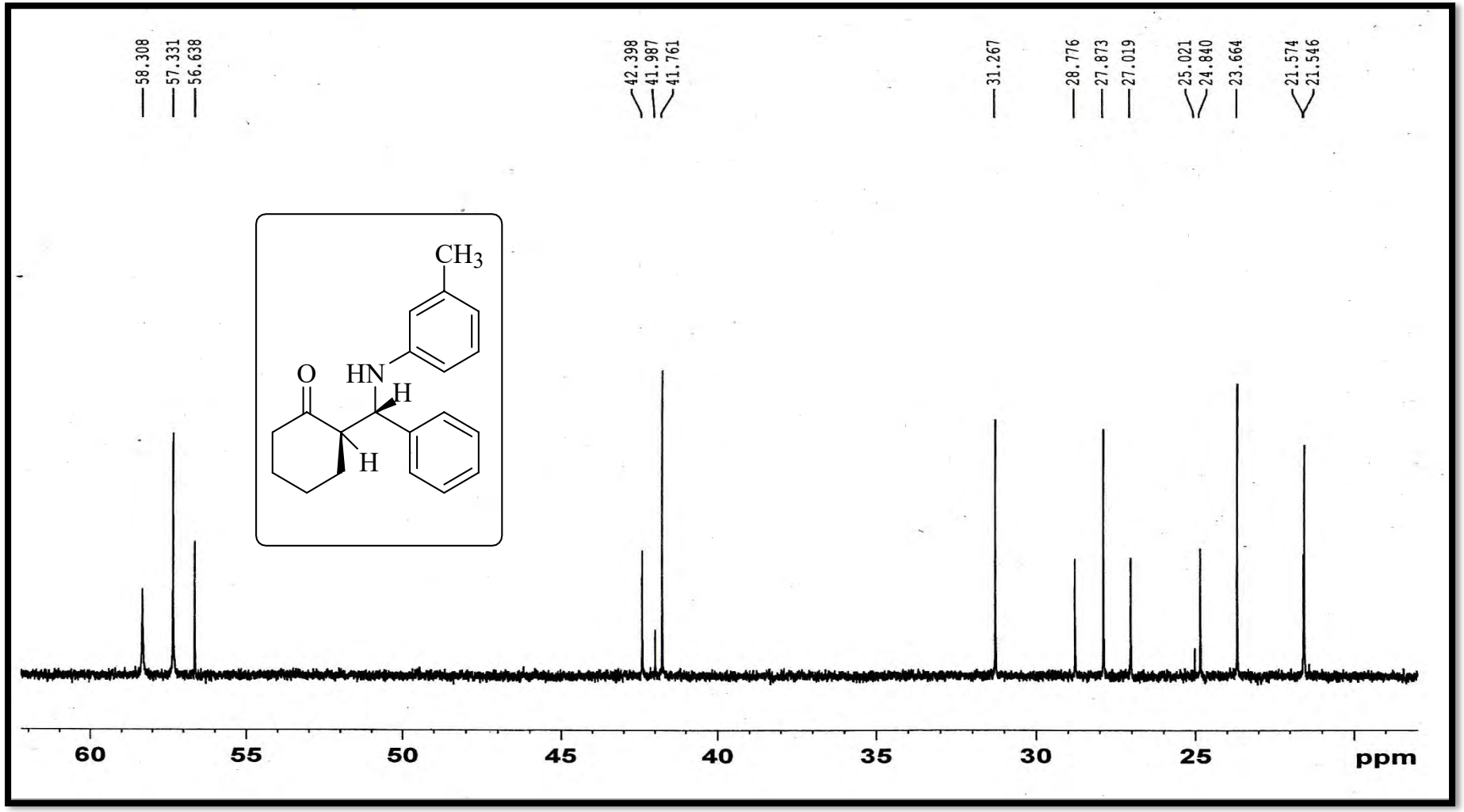


Fig 2.22: ^{13}C-NMR spectrum of synthesized Mannich compound of MB-01

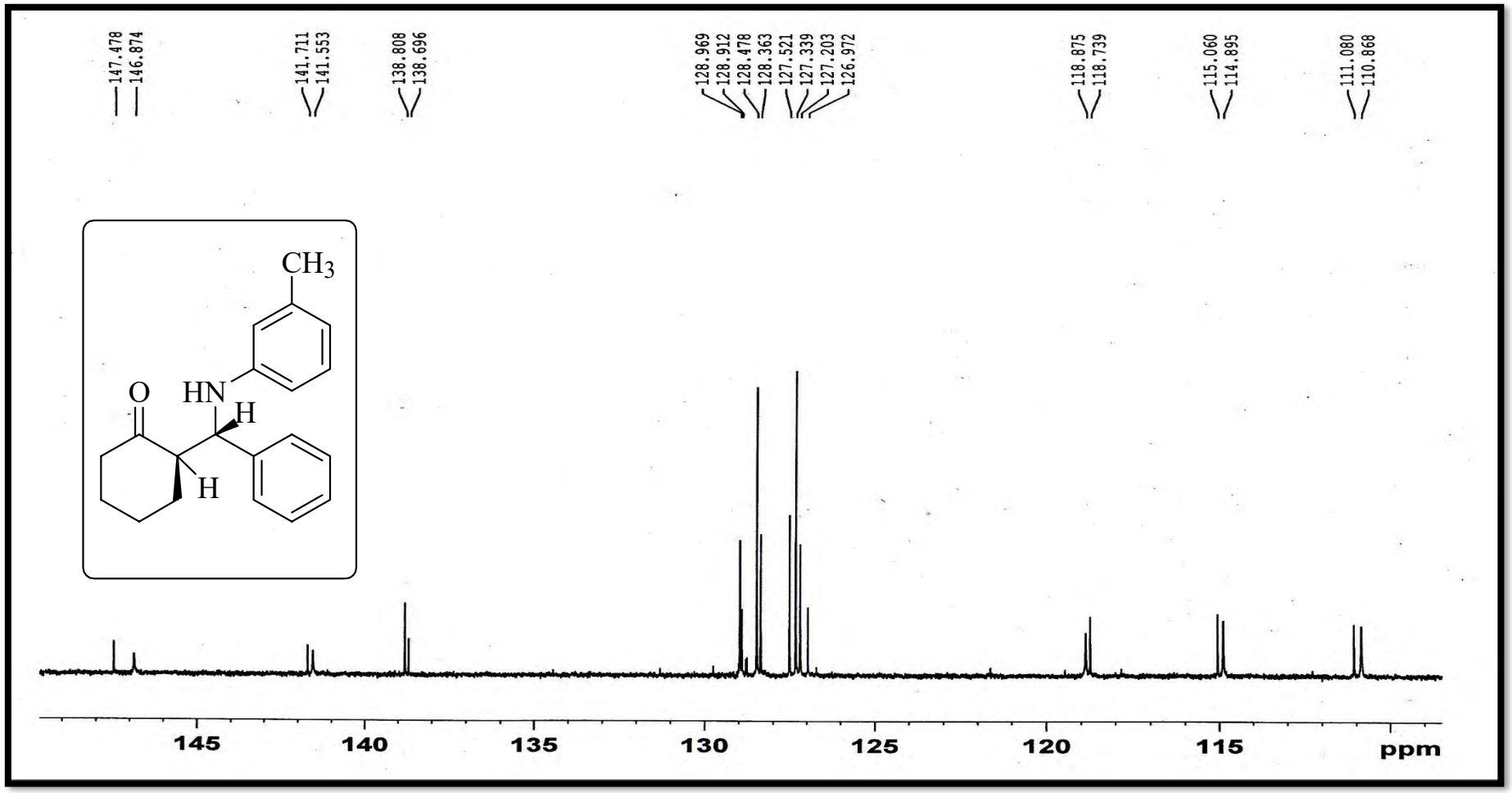


Fig 2.23: ^{13}C-NMR spectrum of synthesized Mannich compound of MB-01

Chapter 3

Biological Evaluation OF IONIC LIQUIDS

CHAPTER 3

Introduction

The development of cleaner technologies is a major emphasis in green chemistry [124]. Among the several aspects of green chemistry, the reduction/replacement of ephemeral organic solvents from the reaction medium is of utmost importance. The use of a large excess of conventional fickle solvents required to conduct a chemical reaction creates ecological and economic concerns. The search for a non-fickle and recyclable alternative is thus holding a key role in this field of research. The use of fused organic salts, consisting of ions, is now emerging as a possible the remaining options. There were some (eco) toxicological and toxicity studies of ILs with bacteria, phytoplankton, freshwater invertebrates and fishes from newly developed ILs [125].

So it is the demand of time with respect their uses in wide field of chemical industries and academia to insure the toxicological profile that includes the antimicrobial activity study of synthesized ILs. The antimicrobial activity study shows and confirms them about their safe uses in any fields. The antimicrobial activity test is the further measurement to require some views of environmental aspects as standard scale of ILs as a green solvent for uses [126]. To carry out the study, some test is very close for experiment such as Screening of antimicrobial activity, Minimum inhibition concentration (MIC) and Minimum bactericidal/fungicidal concentration (MBC/MFC) [127], Evaluating biofilm susceptibility to antimicrobial agents, etc [128-131]. These tests were quizzed in this work and show the relative toxicological profile in view of micro-organism of ILs.

Literature review

In the race to synthesize new pharmaceutical drugs [132], ILs have attracted a great deal of attention amongst in the scientific community due to their variety of potential pharmaceutical applications. ILs represents a big success for industrial and engineering chemistry at the beginning of the 21st century. One of the most appealing features of ILs for pharmaceutical applications is that they are highly customizable materials that can be specially made with pre-selected characteristics by varying the cations and anions of which they are comprised. Combinations of different cations and anions result in various ILs which provide a wide range of hydrophobicity/hydrophilic, acidity/basicity, viscosities, etc. IL strategies can take advantage of the dual nature (discrete ions) to realize enhancements which may include

controlled solubility (e.g., both hydrophilic and hydrophobic ILs are possible, bioavailability or bioactivity, stability, elimination of polymorphism [133], new delivery options (e.g., slow release or the IL-API as „solvent"), or even customized pharmaceutical cocktails. ILs having unique protective metabolic roles can act as antioxidants, protect macromolecules, enhance protein folding and regulate cell volume [134,135].

ILs have also attracted the scientific community"s due to their pharmaceutical properties such as antimicrobial, antiseptic or antifouling actions, acetyl cholinesterase (AChE) inhibition [136,137], AMP (Adenosine mono-phosphate) deaminase inhibition [138], delivery of anti-inflammatory drugs [139], local anesthetic, anti-nociceptive, anticholinergic [140], anticancer activities [141] and in protein formulations [142]. Enzymes suspended in the ILs could be reused three times, with less than 10% loss of activity per cycle without influencing enantion-selectivity [143]. Based on these interesting properties, ILs appears to ready to provide a new research outlook in the field of medicinal chemistry. However, the toxicity of some ILs has not been explored much in applications where this property can be desirable and lead to a variety of pharmaceutical applications [144]. Carson *et al.* have reported the broad spectrum antibioflim activity of 1-alkyl-3-methylimidazolium chloride and other imidazolium based ILs against a variety of clinically important microbes [145]. Therefore, ILs with their tunable properties and toxicities could potentially be designed as anti-cancer, anti-viral and other therapeutic agents [146]. If a therapeutic response were seen, then the major advantage of ILs would be in tuning their toxicity while tailoring the physiochemical and pharmacological properties necessary for the desired therapeutic application [147]. Based on these interesting properties, ILs appears ready to provide a new research outlook in the field of medicinal chemistry.

Antimicrobial Agents

Use of substances with antimicrobial properties is known to have been common practice for at least 2000 years. Ancient Egyptians and ancient Greeks used specific molds and plant extracts to treat infection. More recently, microbiologists such as Louis Pasteur and Jules Francois Joubert observed antagonism between some bacteria and discussed the merits of controlling these interactions in medicine. In 1928, Alexander Fleming became the first to discover a natural antimicrobial fungus known as ***Penicillium rubens*** [148].

The substance extracted from the fungus he named penicillin and in 1942 it was successfully used to treat a ***Streptococcus*** infection. Cellulasesis is extracted from ***penicillium***

janthinellum mutants using solid-state production and their stability in ILs [148]. Penicillin also proved successful in the treatment of many other infectious diseases such as gonorrhea, strep throat and pneumonia, which were potentially fatal to patients up until then, many antimicrobial agents exist, for use against a wide range of infectious diseases. An antimicrobial is an agent that kills microorganisms or inhibits their growth [149]. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against them. For example, antibacterials are used against bacteria and antifungals are used against fungi. They can also be classified according to their function. Agents that kill microbes are called microbicidal, while those that merely inhibit their growth are called biostatic. The use of antimicrobial medicines to treat infection is known as antimicrobial chemotherapy, while the use of antimicrobial medicines to prevent infection is known as antimicrobial prophylaxis [150].

The main classes of antimicrobial agents are disinfectants ("nonselective antimicrobials" such as bleach), which kill a wide range of microbes on non-living surfaces to prevent the spread of illness, antiseptics (which are applied to living tissue and help reduce infection during surgery), and antibiotics (which destroy microorganisms within the body). The term "antibiotic" originally described only those formulations derived from living organisms but is now also applied to synthetic antimicrobials, such as the sulphonamides, or fluoroquinolones [151]. The term also used to be restricted to antibacterials (is often used as a synonym for them by medical professionals and in medical literature), but its context has broadened to include all antimicrobials. Antibacterial agents can be further sub-divided into bactericidal agents, which kill bacteria, and bacteriostatic agents, which slow down or stall bacterial growth [152]. ILs is the new class of the agent of antimicrobial for some diseases under non-profile substance. So the antimicrobial profile has to be developed as a result having probability to obtain a new class of antimicrobial agent.

3.3.1 Anti-bacterials

The discovery, development and clinical use of antibacterials during the 20th century have substantially reduced mortality from bacterial infections. The antibiotic era began with the pneumatic application of nitroglycerine drugs, followed by a “golden” period of discovery from about 1945 to 1970, when a number of structurally diverse and highly effective agents were discovered and developed. However, since 1980 the introduction of new antimicrobial agents for clinical use has declined, in part because of the enormous expense of developing

and testing new drugs. Now bioactive compounds are customized for bacterial targets [153]. Paralleled to this there has been an alarming increase in resistance of bacteria, fungi, viruses and parasites to multiple existing agents [154]. Now ILs are used as the antibacterial and biofilm actives agent [152]. Some imidazinium based ILs is high pharmaceutical ingredients compared to the traditional others [155].

Antibacterials are used to treat bacterial infections. The toxicity to humans and other animals from antibacterials is generally considered low. After prolonged antibacterial use consumption of probiotics and reasonable eating can help to replace destroyed gut flora. Stool transplants may be considered for patients who are having difficulty recovering from prolonged antibiotic treatment, as for recurrent ***Clostridium difficile*** infections [156]. We now wish to report on the antimicrobial and antibioflim activities of a series on 1-alkylquinolinium bromide ILs, against a panel of clinically relevant pathogens, for example, methicillin resistant ***Staphylococcus epidermidis*** (MRSE) and ***Pseudomonas aeruginosa*** [145].

Biological Applications of Ammonium based ILs

The encouraging results of preliminary toxicological studies on ammonium-based ILs provide good opportunities for the development of ILs in biomedical applications. Choline phosphate ILs derivatives have received a great deal of attention due to their pharmacological activity, such as allopurino-ILs [144], which is still the drug of choice for the treatment of hyperurecemia and gouty arthritis. Pyrazolopyrimidine are purine analogues and as such they have useful properties as antimetabolites in purine biochemical reaction. Moreover, these compounds also display marked antitumor and antileukemic activity. Pyrazolopyrimidine derivatives have demonstrated promising antimicrobial activity against gram-positive bacteria [157].

Synthesis of such biologically important compounds assumes great importance. The use of toxic solvents or expensive is catalysis [158-160]. In recent years, the interest in room temperature ILs is increasing as green reaction media for synthetic organic chemistry. It is worth to note that Shingare et al. reported the Knoevenagel condensation reactions in ILs ethyl ammonium nitrate of pyrazolone with few aromatic aldehydes gave moderate to high yields [161]. In continuation of our interest in using ILs as a green reaction medium for the synthesis pyrazolopyrimidine derivatives using 3- methyl-1-phenyl-5-pyrazolone with urea

and various substituted aldehydes in the presence of 2-methyl-3-butylimidazolium chloride as catalyst.

An ionic liquid/aqueous two-phase system based on the hydrophilic ionic liquid 1-butyl-3-methylimidazolium chloride [162] and has been employed for direct extraction of proteins from human body fluids for the first time. Proteins present at low levels were quantitatively extracted into the BmimCl-rich upper phase with a distribution ratio of about 10 between the upper and lower phase and an enrichment factor of extraction of proteins from biological fluids by use of an ionic liquid/aqueous two-phase system. Liquid/liquid extraction-bioconversion processes based on functional ILs are emerging as a great potential, simple, and low-cost method in large-scale protein separation and purification [163]. Enzyme-catalyzed hydrolysis of cellulose in ILs is green approach toward the production of biofuels media by the biodegradation through the microorganism [164]. ILs are used as enzymatic catalysis of formation of Z-aspartame, an alternative to enzymatic catalysis in organic solvents [165]. Compatible ionic liquid-celluloses system is for hydrolysis of lignocelluloses biomass [166].

Methods for antimicrobial activity evaluation of ILs

A number of methods exist for the accurate determination of microbial susceptibility to antimicrobial/antibiotic compounds. Such methods yield vital data regarding fundamental sensitivity or tolerance to a given antimicrobial biocide or antibiotic and are therefore vital to the successful treatment and management of microbial infections. Furthermore, such tests are useful for determining relative potency of an antimicrobial agent across a range of species and for identifying antimicrobial synergies. The basic testing procedures, which have been used in the assessment of the antimicrobial activity of ILs, are considered as basic planktonic susceptibility assays (MIC or MBC/MFC) or agar diffusion techniques. Anti-microbial susceptibility testing methods the following three methods have been shown to consistently provide reproducible and repeatable results when followed correctly.

Disc diffusion method

Disc diffusion refers to the diffusion of an antimicrobial agent of a specified concentration from discs, tablets or strips, into the solid culture medium that has been seeded with the selected inoculums isolated in a pure culture. Disc diffusion is based on the determination of

an inhibition zone proportional to the bacterial susceptibility to the antimicrobial present in the disc. The diffusion of the antimicrobial agent into the seeded culture media results in a gradient of the antimicrobial. When the concentration of the antimicrobial becomes so diluted that it can no longer inhibit the growth of the test bacterium, the zone of inhibition is demarcated. The diameter of this zone of inhibition around the antimicrobial disc is related to MIC for that particular bacterium/antimicrobial combination; the zone of inhibition correlates inversely with the MIC of the test bacterium. Generally, the larger the zone of inhibition, the lower the concentration of antimicrobial required to inhibit the growth of the organisms. However, this depends on the concentration of antibiotic in the disc and its infusibility.

Broth and agar dilution method

The aim of the broth and agar dilution methods is to determine the lowest concentration of the assayed antimicrobial that inhibits the visible growth of the bacterium being tested (MIC, usually expressed in µg/mL or mg/L). However, the MIC does not always represent an absolute value. The „true" MIC is a point between the lowest test concentration that inhibits the growth of the bacterium and the next lower test concentration. Therefore, MIC determinations performed using a dilution series may be considered to have an inherent variation of one dilution.

Anti-microbial ranges should encompass both the interpretive criteria (susceptible, intermediate and resistant) for a specific bacterium/antibiotic combination and appropriate quality control reference organisms. Antimicrobial susceptibility dilution methods appear to be more reproducible and quantitative than agar disc diffusion. However, antibiotics are usually tested in doubling dilutions, which can produce inexact MIC data. Any laboratory that intends to use a dilution method and set up its own reagents and antibiotic dilutions should have the ability to obtain, prepare and maintain appropriate stock solutions of reagent-grade antimicrobials and to generate working dilutions on a regular basis. It is then essential that such laboratories use quality control organisms to assure accuracy and standardization of their procedures.

Agar diffusion method

The agar diffusion technique (also known as the Kirby-Bauer test [167] but described somewhat earlier by Abraham am co-workers in 1941 [168] is a simple and commonly employed technique for determination of MIC on solid media. The basic method requires antibiotic/biocide impregnated discs to be placed on the surface of agar plates seeded or spread with the appropriate test strain of bacteria or fungi. Antimicrobial agent may also be added (as a solution) to wells punched in the agar. The diffusion of antimicrobial agent into the surrounding agar results in inhibition of growth around the reservoir/source and gives rise to zones or clearance where (for sensitive organisms) microbial growth is inhibited. Generally, the diameter of these zones of inhibition or clearance increases with increasing concentration of antimicrobial agent, and this may be measured to determine qualitatively the relative degree of toxicity.

The technique is also useful for empirical determination of antimicrobial activity of a given compound or assessing relative antimicrobial potency by measuring zones of inhibition of bacterial or fungal growth around the antimicrobial site of application. Few years ago, this method has been championed by Stephens and co-workers [169] as a simple method for rapid determination of relative toxicity of ILs. This simple, inexpensive method has been suggested as a basic requirement in the toxicological assessment of ILs and, since it requires neither specialist equipment nor advanced microbiological techniques, may be performed routinely in laboratories conducting research into ionic liquids with minimum microbiological expertise. Despite this, the use of agar diffusion assays will provide basic toxicity information for a large number of ILs and provides a rapid, high-throughput „first look" in the hierarchical screening of antimicrobial activity of ILs [170].

Dilution method

Dilution tests are routinely used for the determination of the two most fundamental parameters in antimicrobial susceptibility testing; the minimum biofilm eradication concentration (MIC) and the minimum bactericidal/fungicidal concentration (MBC/MFC), sometimes referred to as the minimum lethal concentration (MLC). Dilution tests usually involve the use of liquid media but agar may also be used (as discussed above).

Doubling dilutions of the antimicrobial agent are prepared and added to a defined inoculum of test microorganism taken from the logarithmic phase of growth, such that a final inoculum of 5×10^5 colony forming units (CFU or viable cells)/ml is achieved. Following incubation at $35^\circ \pm 2.5^\circ$C overnight (18 hours), the MIC is determined as the concentration of antimicrobial

contained in the first clear tube/well. Therefore, the MIC is defined as the minimum concentration of antimicrobial agent that inhibits the growth of an overnight culture of micro-organism.

Antibacterial Working Procedure

Chemicals and Equipment

ILs are used as test chemical for antibacterial work and different concentrations were prepared using serial dilution technique taking one initial concentration as higher (1000 mM). Chemicals were dissolved in water or other suitable solvents, and they act as positive control. Nutrient agar was prepared according to the instruction leveled in the container and kept in freezer for longer use. Dilute alcohol or acetone were used to ensure for septic environment during the culture preparation and bacterial inoculation. Laminar Air flow was confirmed all the time during the culture preparation and all the tests conducted. Incubator for bacterial growth was maintained at temperature 37 ±1 $^{\circ}$C.

Preparation of Bacterial Inoculums

The Gram Positive and Gram Negative bacteria were pre-cultured in Nutrient Broth (NB) on overnight in incubator at 37 $^{\circ}$C. After incubation centrifuged at 10,000 rpm for 5 min, pellet was suspended in distilled water (DW). The Petri dishes were flooded, 50 mL of sterile distilled water, using sterile cotton buds, micro tips and forceps.

Preparation of IL solutions in different concentrations

The required amount of the sample was measured in digital balance with highly carefully so that no impurities were obtained. Then the required 1 ml distilled water was added and well shake for well soluble. Some of samples were not soluble in water. These are soluble in MeOH so that, methanol was required solvent for these samples.

Table 5.1: List of ILs and the required weight for 1 M solution.

Code no.	M. Wt.	Req. Wt.(g)
K-IL:01(09)	175.25	0.175
K-IL:02(10)	189.26	0.189
K-IL:03(11)	203.27	0.203
K-IL:04(12)	217.28	0.217
K-IL:05(13)	289.27	0.289
K-IL:06(14)	328.22	0.328
K-IL:07(15)	269.75	0.269

Antibacterial Screening via Well diffusion test

Media was spread in petri-plate at first and keep 40 minutes for solidification of media. Then bacterial inoculum was uniformly spread using sterile cotton swab or hockey stick on a sterile Petri dish Nutrient Agar media. Four serial wholes were made. Then four different compounds of 20 µL with solution were taken in each whole in marking on petri-plate. 20 µL of sample solution were added to each of the 3 wells (5 mm diameter holes cut in the agar gel, 40 mm apart from one another). Each plate contained a control as water or methanol with respect to solubility of solvent. The systems were incubated for 24 hours at 36 ±1 ºC, under aerobic conditions. After incubation, confluent bacterial growth was observed. Inhibition of the bacterial growth was measured in mm.

3.7 Results from Antibacterial Screening

Antibacterial screening of the test ILs were carried out with six bacterial pathogens, such as, ***Bacillus cereus, Staphyllococcus aureus, Eschericia coli, Salmonella typhi, Psedomonous aeroginosa and Sarcina lutea.*** The bacterial inhibition zone (subtracting the well diameter 5.0 mm) was measured in mm. All the measurements were done in triplicate and the averages were listed in Table 5.2.

The initial concentration was maintained for all ILs in 75% (w/v) in distilled water or methanol. A control plate is always observed for the ILs if there is any significant inhibition

occurred for the solvent. The results showed that all compounds had antimicrobial activity against bacterial pathogens used in this study.

Table 5.2: Zone of inhibition from the tested ILs.

List of pathogens & ILs	**K-IL:01 (09)**	**K-IL:02 (10)**	**K-IL:03 (11)**	**K-IL:04 (12)**	**K-IL:05 (13)**	**K-IL:06 (14)**	**K-IL:07 (15)**
Bacillus cereus (+)	06	07	03	04	**1 0**	08	07
Staphylococcus aureus (+)	05	05	04	08	**09**	09	08
Sarcina lutea (+)	07	02	08	07	**10**	05	04
Salmonella typhi (-)	06	03	05	06	**09**	06	09
Eschericia coli (-)	**09**	**05**	**10**	**12**	**13**	**11**	**08**
Pseudomonas aeruginosa (-)	07	07	05	06	**08**	09	08

After getting information from the screening, the chemicals were then proceeded for antibacterial assessment with three different concentrations, 1000, 500 and 100 mM using well diffusion method.

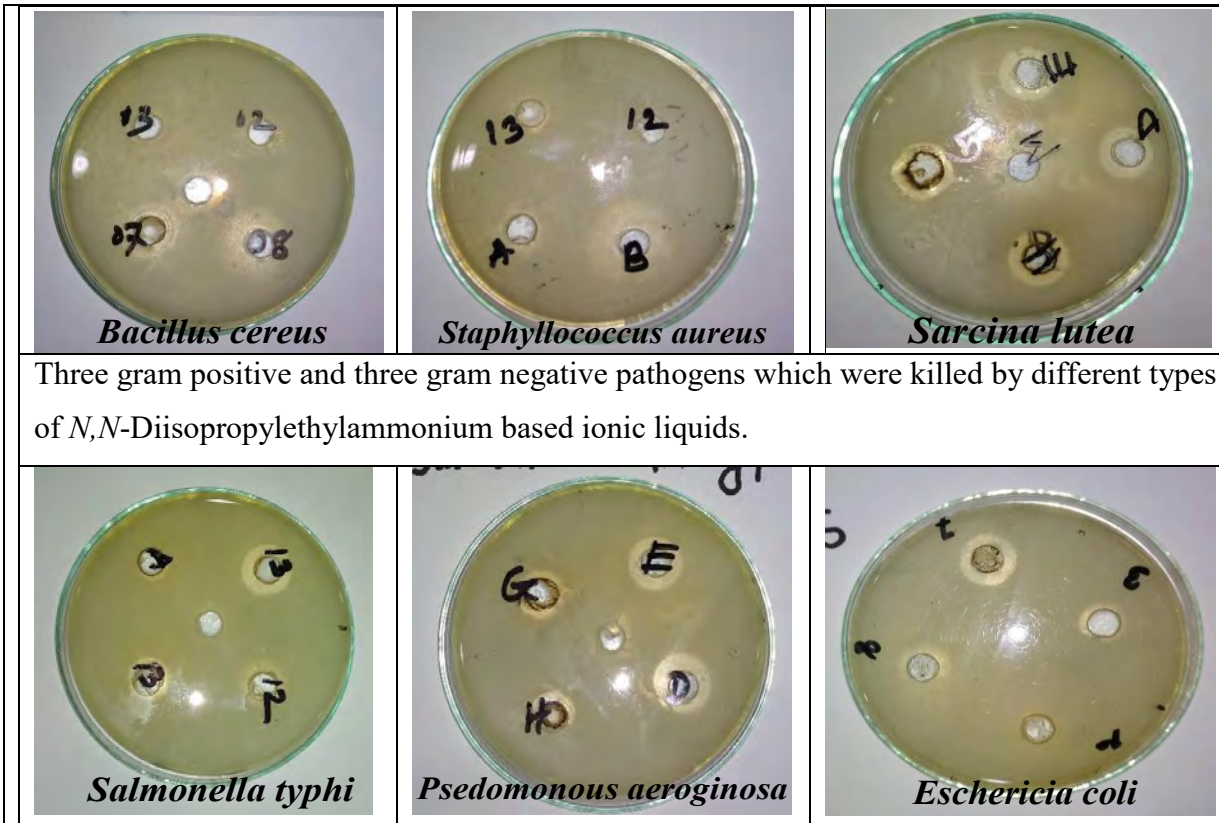


Fig: Zone of inhibition from the tested of different Ammonium based ILs.

Seven (07) different ILs, 05 of them showed zone of inhibition or activity below 500 mM, which were then selected for MIC evaluation. MIC for the tested ILs were calculated from the inhibitions showed in the concentrations, such as, 1000, 750, 500, 375, 187.5 and 93.75 mM using the well diffusion technique. The results were discussed in terms of the effect of ILs concentration, aromaticity and functionality in their structure.

Effect of concentration

The antimicrobial activity of ILs of different concentrations against six bacteria indicates that, the higher activity was found on ***E. coli*** bacteria for all compounds. The activity of a compound is to be as ***E. coli*** is higher than others. The lower activity of compound is in ***P. aeruginosa*** and ***S. aureus***. In higher concentration (1000 m M), almost all the compounds showed the activity, whereas the trend is reduced in 500 mM and 05 ILs showed the activity against the bacterial pathogens.

Effect of Anions

In the toxicological study, anions have an importance role in light of molecular weight due to increase the side chain view of the both the aliphatic or aromatic chain. The changes of anion reflect in antibacterial and antifungal activities, which were presented in results and discussion in this chapter with graph below.

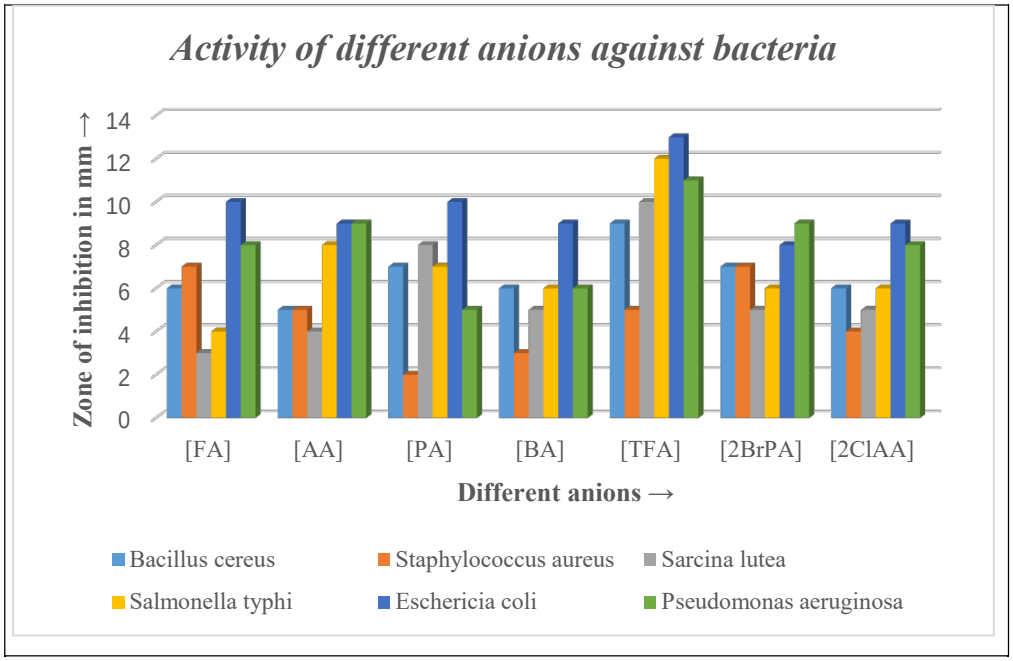


Figure 5.1: Activity of different anions.

3.8 Summary

This chapter consists of microbial analysis from the synthesized seven 07 ILs using six bacterial pathogens and two fungal strain. Antibacterial screening, full test, MIC evaluation assay were described according to the standard procedures.

Chapter 4

CATALYTIC EFFECT OF SYNTHESIZED ILs

MANNICH & ESTERIFICATION REACTION

CHAPTER 4

MANNIC REACTION

Introduction

Mannich reaction is one of the most important C-C bond forming reactions in organic synthesis for the preparation of secondary and tertiary amine derivatives [171]. These amines are further used for the synthesis of many intermediates, biologically active and natural products such as alkaloids and polypeptides [172]. The products of Mannich reaction are mainly β-amino carbonyl compounds and its derivatives that are used for the synthesis of amino alcohols, peptides, lactums and as precursors to optically active amino acids [173]. The conventional catalysts for classical Mannich reaction of aldehydes, ketones and amines involve mainly organic and mineral acids like proline [174], acetic acid [175], p-dodecylbenzenesulfonic acid [176] and some Lewis acids [177, 178]. They often suffer from the drawbacks of long reaction times and harsh reaction conditions, toxicity and difficulty in product separation, which limit its use in the synthesis of complex molecules. The most frequently used promoters like Lewis acid catalysts [179], Bronsted acid catalysts [180, 181] and Lewis base catalysts [182] have been reported to catalyze Mannich reaction. Scandium triflate, copper triflate, scandium tris(dodecylsulfate) and scandium tris(dodecanesulfonate) [183], $InCl_3$ [184] and HBF_4 [185] have also been known to catalyze these reactions in good yields with the aid of surfactant only. Lanthanide triflate in solvents like dichloromethane and acetonitrile have also been known to catalyze Mannich reaction [186, 187].

As there is a growing demand for the development of organic reactions in environment friendly media, synthetic manipulations have to be made to minimize the use of hazardous chemicals like replacing the traditional organic solvents in reactions and their subsequent workup with other non-toxic solvents like water or super critical CO_2. In this context Akiyama et al. [180, 181] have reported Mannich type reactions in aqueous media. Ionic liquids have attracted extensive research interest in recent years as environmentally benign solvents due to their favorable properties like non-inflammability, negligible vapor pressure, reusability and high thermal stability [188, 189]. They have also been referred to as „designer solvents" as their physical and chemical properties could be adjusted by a careful choice of cation and anion. Apart from this they exhibit acidic properties. Combining these unique properties of ionic liquids, they are emerging as a "green reaction media" (catalyst + solvent). The use of ionic liquids as reaction medium may offer a convenient solution to both the solvent emission

and catalytic recycling problem [190-192]. Among the different Mannich type reactions reported, the reaction of silyl enolates with aldimines have been reported in ionic liquids [180]. Ruthenium complexes and ytterbium (III) triflate catalyzed Mannich reaction in Bmim[PF_6] have been reported [194, 195]. Mannich reaction using Bronsted acid ionic liquids as catalysts and solvent have also been reported [196].

Our recent interest has been in the development of new synthetic methods on using ionic liquids as reaction media [197]. Herein as a part of the program to investigate the different organic reactions feasible in Bronsted acid ionic liquids, we report a simple and fast reaction of different aldehydes, ketones and amines to afford corresponding β-amino carbonyl compounds. To the best of our knowledge in the open literature, Mannich reaction involving catalytic amount of ionic liquids bearing triphenyl phosphonium sultone/ immidazolium sultone as cation and TFA/PTSA as anion are unprecedented. The reaction proceeded very fast with high yield of the desired Mannich base using catalytic amount of ionic liquid. The effect of anions and cations of the ionic liquid on the reaction rate has also been investigated [198].

Experimental

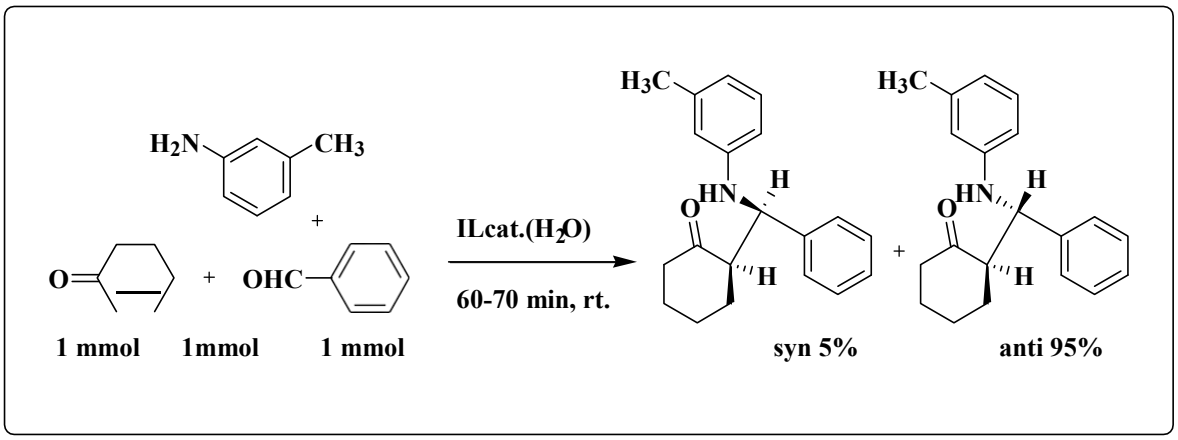
Chemicals

All the aldehydes, ketones, amines, were obtained from S.D. Fine Chemicals, Mumbai. Trifluoroacetic acid (TFA) was obtained from Fluka Chemicals and *N,N*-Diisopropylethylamine, was obtained from Loba Chemie, India and used without further purification.

Mannich reaction: a typical procedure

In a typical reaction, benzaldehyde (1 mmol), 3-methylaniline (1 mmol), cyclo-hexanone (1.1 mmol), and ionic liquids (0.20 g) as catalysts and solvent were stirred at room temperature (25 $^{\circ}$C) in a round-bottomed flask. After a certain time, the reaction mixture became viscous and solidified. At this stage the time was noted and the ionic liquid was separated from the reaction mixture by extraction with distilled water (5× 3 ml). The ILs being soluble in water comes in the water layer. The solid was separated by filtration and product was recrystallized from 98% ethanol and vacuum dried for 5 h. The product was identified using ^{1}H NMR in $CDCl_3$ with TMS as reference (400 MHz) and by FT-IR on a Shimadzu (model 8201 PC) spectro-photometer using KBr plates in a frequency range. The ionic liquid in the filtrate was separated from the unreacted starting materials by extracting the filtrate with ether. Then the

water layer containing ionic liquid was vacuum dried at 70 °C for 5 h to remove water and the ionic liquid was reused.



Scheme 1: Reaction scheme for Mannich reaction of cyclohexanone, benzaldehyde and 3-methylaniline.

Results and discussion

The Mannich reaction of aldehydes, ketones and amines in presence of Bronsted acidic ionic liquids was conducted at room temperature and the results are summarized in Table 1. No Mannich basewais observed in the absence of ionic liquids (Table 1, entry 1). Mannich reaction with TFA in ethanol (2.5 g) gave a yield of 57 % (Table 1, entries 2). The study showed that catalytic amount of ionic liquids bearing *N, N*-Diisopropylethyl ammonium trifluoroacetate as anion catalyzed Mannich reaction in very less time and gives high isolated yield. All the above ionic liquids are suitable for Mannich reaction, however, catalytic amount of *N,N*-Diisopropylethyl ammonium trifluoroacetate [DIPEAH][TFA], a solid at room temperature, gave the highest yield in very less time compared to other ionic liquids studied (Table 1, entry 4).

Table 1: Results of Mannich reaction with different ILs.

Entry	Ionic Liquids	Time (h)	Yield (%)
1	Nil	10	0
2	TFA[a](0.06)	4	57
3	PTSA[a](0.1)	4	55
4	[PyH][TFA] (0.20)	10 min	91
5	[ANPyH][TFA] (0.25)	20 min	93
6	[DMAPyH][TFA] (0.23)	30 min	85
7	**[DIPEAH][TFA] (0.23)**	**1**	**92.7**

Reaction condition: aldehyde:amine:cyclohexanone, (1:1:1) mole ratio; temperature at 25 ^{0}C; Two drops of water (0.06g) was added to the ionic liquid to allow proper mixing.

[a] No water was added. Reaction with PTSA and TFA was carried out using 2.5g of ethanol.

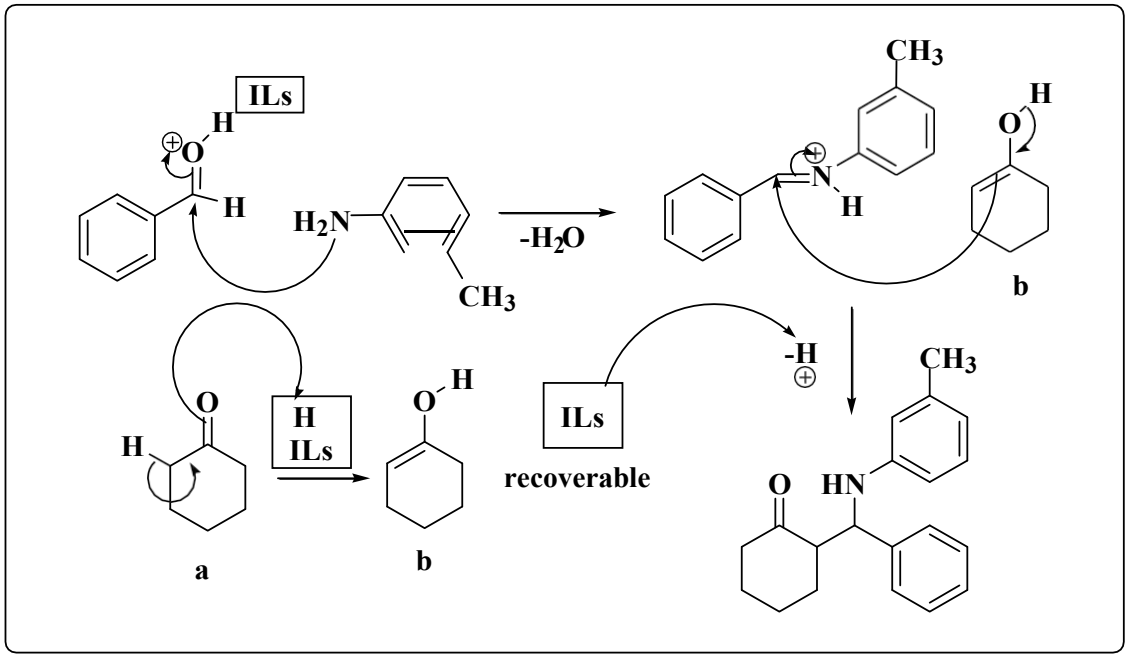
To optimize the reaction conditions, Mannich reaction was carried out with benzaldehyde, 3-methylaniline and cyclohexanone (Scheme 1) using [DIPEAH][TFA] (1 mmol, 0.20 g), solid at room temperature), which gave a yield of 91% (Table 1, entry 4). However, on increasing the amount of [DIPEAH][TFA] (1.1 mmol, 0.23 g), the yield increased to 92.7% only (Table 1, entry 7). All the ionic liquids were easily recyclable after removing starting materials and water. [DIPEAH][TFA] was recycled four times for the reaction of benzaldehyde, 3-methylaniline and cyclohexanone (Table 2).

Table 2: Catalyst recycling of ionic liquid for Mannich reaction.

Entry	Cycle	Mannich base, % Yield
1	Fresh	92.7
2	1st recycle	90
3	2nd recycle	89
4	3rd recycle	89
5	4th recycle	88

Reaction condition: aldehyde:amine:cyclohexanone, (1:1:1) mole ratio; temperature at 25 $^{\circ}$C; Two drops of water (0.06g) was added to the ionic liquid to allow proper mixing.

Even after four recycles, product was obtained with similar yield and purity of those obtained in the first recycle. The ionic liquid is retained its structure even after four times recycle as confirmed by NMR spectroscopy.



Scheme 2: Proposed mechanism of Mannich-type reaction in presence of PILs.

Conclusion

In summary, this study evaluates the effect of very small amount of ammonium based ionic liquids as potential catalysts for Mannich reaction of aldehydes, amines and ketones. This work shows that the yields are much improved and the reaction is much faster in this particular ionic liquid, which we hav e used and recovery of the ionic liquid from the reaction mixture is possible by simple extraction with water. This method avoids the use of acid catalysts and environmentally unfavorable volatile organic solvents.

The most attractive part of this work is that only small amount of ionic liquid can catalyze this one-pot three component Mannich type reactions of aldehydes, amines and ketones in water at room temperature and the catalysts were re-used at least four times without loss of their high catalytic activity. The simple experimental procedure, fast reaction, easy product separation and reuse of ionic liquids makes the use of the above ionic liquid a greener and economically viable catalyst for the synthesis of β-amino carbonyl compounds compared with the traditional protocols.

ESTERIFICATION REACTION

Introduction

Fischer esterification a special type of esterification by refluxing a carboxylic a cid and an alcohol in the presence of an acid catalyst. The reaction was first described by Emil Fischer and Arthur Speier in 1895 [199]. Most carboxylic acids are suitable for the reaction, but the alcohol should generally be a primary or secondary alkyl. Tertiary alcohols are prone to elimination. Contrary to common misconception found in organic chemistry textbooks, phenols can also be esterified to give good to near quantitative yield of products [200-201]. Commonly used catalysts for a Fischer esterification include sulfuric acid, tosylic acid, and Lewis acids such as scandium(III)triflate. For more valuable or sensitive substrates (for example, biomaterials), dicyclohexylcarbodiimide is often used. The reaction is often carried out without a solvent (particularly when a large reagent excess of alcohol is used) or in a non-polar solvent (e.g. toluene) to facilitate the Dean-Stark method [202]. Typical reaction times vary from 1–10 hours at temperatures of 60-110 °C.

Direct acylations of alcohols with carboxylic acids is preferred over acylations with anhydrides (poor atom economy) or acid chlorides(moisture sensitive). The main disadvantage of direct acylation is the unfavorable chemical equilibrium that must be remedied (e.g. by a large excess of one of the reagents), or by the removal of water (e.g. by using Dean-Stark distillation, anhydrous salts, [203] molecular sieves, or by using a stoichiometric quantity of acid catalyst).

Overview

Fischer esterify cation is an example of nucleophilic acyl substitution based on the electrophilicity of the carbonyl carbon and the nucleophilicity of an alcohol. However, carboxylic acids tend to be less reactive than esters as electrophiles. Additionally, in dilute neutral solutions they tend to be deprotonated anions (and thus unreactive as electrophiles). Though very kinetically slow without any catalysts (most esters are metastable), pure esters will tend to spontaneously hydrolyze in the presence of water, so when carried out "unaided", high yields for this reaction is quite unfavorable.

Several steps can be taken to turn this unfavorable reaction into a favorable one [202].

The reaction mechanism for this reaction has several steps:

- Proton transfer from acid catalyst to carbonyl oxygen increases electrophilicity of carbonyl carbon.
- The carbonyl carbon is then attacked by the nucleophilic oxygen atom of the alcohol.
- Proton transfer from the oxonium ion to a second molecule of the alcohol gives an activated complex
- Protonation of one of the hydroxyl groups of the activated complex gives a new oxonium ion.
- Loss of water from this oxonium ion and subsequent deprotonation gives the ester.

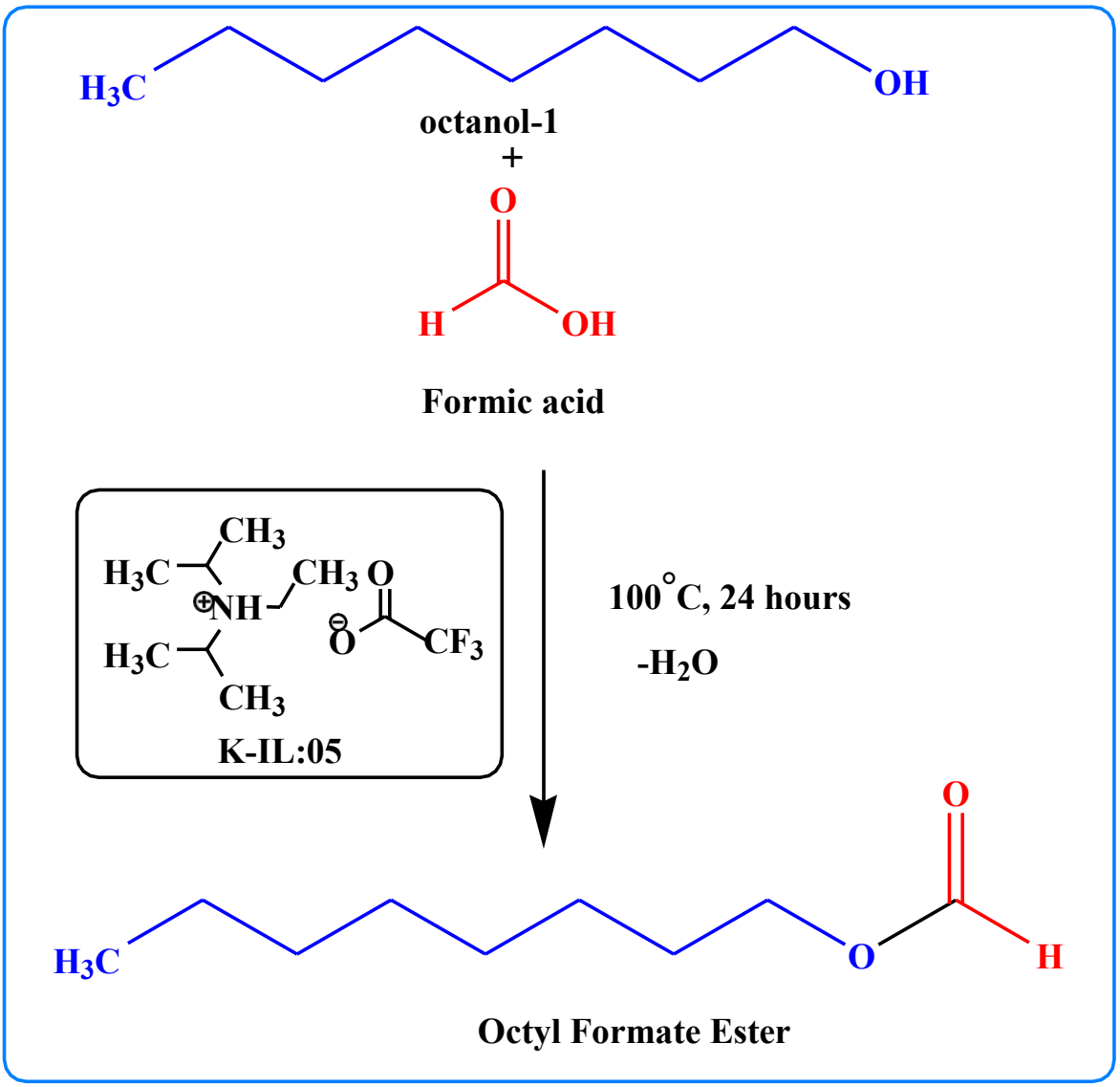
A generic mechanism for an acid Fischer esterification is shown below.

Experimental

Esterification: a typical procedure

In the esterification reaction, octylalcohol 10 mmol and formic acid 10 mmol (equimolar amounts) and **K-IL: 05(13)** ionic liquids (0.20 mL) as catalysts were taken into a round bottomed flask at 100 $^{\circ}$C for 24 hours. The progress of the reaction was monitored by TLC. At the end of the reaction, the mixture was left to cool. The reaction mixture was neutralized by the saturated solution of sodium bicarbonate. The pH was checked with pH paper, the indicated value was below 7, showing that not all the formic acid was neutralized. Solid sodium bicarbonate was added until the pH became weakly alkaline, indicated by the pH paper. The reaction mixture was filtered and washed with distilled H_2O. The sodium salt of the formic acid was found in the water phase and the obtained ester was in the organic phase. The ionic liquid and unreacted formic acid were separated from the reaction mixture by extraction with distilled water (5× 3 mL). The ionic liquid is being soluble in water, so it came in the water layer. Ester was separated by solvent extraction and vacuum dried for 5 h.

The product was identified using ^{1}H NMR in $CDCl_3$ with TMS as reference (400 MHz) and by FT-IR on a Shimadzu (model 8201 PC) spectro-photometer using KBr plates in a frequency range. The ionic liquid in the filtrate was separated from the unreacted starting materials by extracting the filtrate with ether. Then the water layer containing ionic liquid was vacuum dried at 70 $^{\circ}$C for 5 h to remove water and the ionic liquid was reused.



Scheme: Synthesis of Octyl formate ester by using k-IL:05.

Summary:

The synthesized ester was developed from the reaction of octanol and formic acid under mild condition and catalyzed by K-IL(05). This reaction was proceeding by easy methodology. Synthesized ester was characterized by spectral data of (FT-IR and NMR) spectroscopy.

CONCLUSION OF THIS DISSERTATION

Conclusion

In this study, some quaternary ammonium ILs were synthesized, which were relatively cheap and easy to prepare among others. This study was impertinent to include total seven (IL01 to IL7) ILs for their toxicity study using ***N,N*-Diisopropylethylamine** as cation source with seven different aliphatic carboxylic acids as anion sources. The acids include carboxylic acid such as formic acid, acetic acid, propionic acid, butyric acid, trifluoro acetic acid and 2-bromo propionic acid, chloroacetic acid. In the pathway of the **Brønsted** acid base neutralization reaction, protonation was occurred with reflux for approx. 6-8 hours, maintaining the continuous stirring and inert nitrogen environment and gives a good percentage of yields (84-93) % by using small amount of solvent on the light of green chemistry. The synthesized ILs were found to be in liquids state at RT. Many of the liquid ILs were found to be very thick and viscous. The synthesized ILs were characterized by Fourier Transform Infrared Spectroscopy (FT-IR), Nuclear Magnetic Resonance (^{1}H-NMR) Spectroscopy.

The work described in this dissertation concerns the synthesis of different ammonium based ILs due to their bioactivity, developed the toxicity profiles which are used as the alternative of traditional organic solvents and one of the valuable protic ionic liquid such as ***N,N*-Diisopropylethylammonium trifluoroacetate K-IL: 05(13)** was used as acid catalyst in Mannich reaction to form a new class of β-amino carbonyl compounds. K-IL:05 shows another important catalytic effect of formation of typical ester in organic synthesis as an easy method.

Ammonium based ILs are the most important due to their low toxicity and the low cost price in present time.

Antibacterial screening was conducted using the well-diffusion technique with ILs solutions of three different concentrations. The results were then used to select the initial higher concentration for dilution method, to obtain the concentrations as 1000,750, 500, 375, 187.5 and 93.75 mM and finally to measure minimum inhibitory concentration (MIC). The antifungal activity was tested against two phytopathogenic fungi, such as, ***Aspergillus niger*** and ***Rhizoplus azzahra*** using well diffusion susceptibility test. Some of synthesized ILs showed high inhibition as potential antimicrobial agents, can proceed to future study.

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