NOVEL MULTI-CATIONIC IMIDAZOLIUM AND BENZIMIDAZOLIUM BASED IONIC LIQUIDS: SYNTHESIS AND APPLICATIONS FOR ANTIBACTERIAL AND BIODEGRADABLE SURFACTANTS

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ABSTRACT

Ionic liquids as neoteric compounds exhibit many interesting properties, which make them suitable for broad practical applications of industrial and medical applications. Therefore, in current thesis work several novel series of di, tri and tetra-cationic ionic liquids based on imidazolium and benzimidazolium were synthesized simply from readily available starting materials in high yield. Their structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR, and high resolution mass spectroscopy as well as ^{19}F-NMR when necessary. Variations of the synthesized ionic liquid molecular structures led to different applications in life science. The antibacterial activities of bis-imidazolium and benzimidazolium ionic liquids were screened against standard strains of Gram positive and Gram negative bacteria using the micro-broth dilution assay. Most of the studied di-cationic ionic liquids showed promising activities against both types of bacteria due to their high solubility in water in addition to incorporating to sulphonamide moiety. Biodegradability and surfactants properties of tris and tetrakis for both imidazolium and benzimidazolium ionic liquids were investigated. 'Closed-Bottle Test' OECD 301D with sodium *n*-dodecyl sulphate (SDS) as a reference, optical polarizing microscopy and systematic surface tension measurements of aqueous solutions were used for evaluation of their physical behaviour. Some ionic liquids showed assembly behaviour in pure form (*i.e.* absence of solvent) and in the presence of polar or nonpolar solvents. These surfactants of both imidazolium and benzimidazolium ionic liquids effectively reduced the surface tension of water in the range of 28–34 mN m^{-1}. The incorporation of tri- and tetra alkyl or phenyl side chains into imidazolium and bezimidazolium ionic liquids with tri and tetra-ester groups, significantly improved the biodegradation. The linear alkyl side chains (*i.e.* butyl, hexyl, octyl, decyl and dodecyl) in both imidazolium and benzimidazolium ionic liquids series promoted an increase in biodegradation and phase behaviour results as compared to aromatic side-chains.

ABSTRAK

Cecair ionik seperti sebatian neoterik mempamerkan banyak sifat yang menarik, menjadikannya sesuai untuk aplikasi praktikal yang luas bagi aplikasi industri dan perubatan. Oleh sebab itu, dalam tesis ini, beberapa siri bagi di, tri dan tetra-kation cecair ionik berasaskan imidazolium dan benzimidazolium telah disintesis hanya daripada bahan sedia ada dalam hasil yang tinggi. Struktur tersebut telah disahkan dengan ^{1}H-NMR, ^{13}C-NMR, FT-IR dan spektroskopi jisim resolusi tinggi begitu juga ^{19}F-NMR apabila perlu. Kepelbagaian struktur molekul bagi cecair ionik disintesis mengarah kepada aplikasi berbeza dalam sains hayat. Aktiviti antibakteria bagi cecair ionik bis-imidazolium dan benzimidazolium telah diskrin terhadap strain piawai bakteria positif Gram dan negatif Gram menggunakan ujian mikro-sup pencairan assay. Kebanyakan cecair ionik-kation yang dikaji menunjukkan aktiviti yang berpotensi terhadap kedua-dua jenis bakteria kerana kebolehlarutan yang tinggi dalam air dalam tambahan kepada gabungan moieti sulfonamida. Sifat biodegrabiliti dan surfaktan bagi tris dan tetrakis untuk kedua-dua cecair ionik imidazolium dan benzimidazolium telah dikaji. Ujian 'Botol-Tertutup' OECD 301D dengan sodium n-dodecyl sulfat (SDS) sebagai rujukan, mikroskopi polarisasi optik dan pengukuran tegangan permukaan sistematik bagi larutan akueus digunakan untuk menilai kelakuan fizikalnya. Beberapa cecair ionik menunjukkan sifat himpunan dalam bentuk asli (misalnya ketidakhadiran pelarut) dan dengan kehadiran pelarut berpolar dan tidak berpolar. Surfaktan bagi kedua-dua cecair ionik imidazolium dan benzimidazolium mengurangkan tegangan permukaan air secara berkesan dalam julat 28-34 mN m^{-1}. Gabungan tri dan tetra alkil atau rantaian sisi fenil kepada cecair ionik dalam imidazolium dan benzimidazolium dengan kumpulan tri dan tetra alkil, berkepentingan memperbaiki biodegradasi. Rantaian sisi alkil linear (misalnya butil, hexil, octil, decil dan dodecil) dalam kedua-dua siri cecair ionik imidazolium dan benzimidazolium

menggalakkan peningkatan dalam hasil biodegradasi dan sifat fasa berbanding rantaian-sisi aromatik.

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Finally, I dedicate my achievements to my mother soul that I keep feeling her around.

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LIST OF SYMBOLS AND ABBREVIATIONS

˚C	Degree Celsius
Å	Angstrom
bmim	1-Butyl-3-methylimidazolium
BOD	Biochemical oxygen demand
BOD_5	Biochemical oxygen demand over 5 days
bs	Broad singlet
bt~s	Broad triplet about singlet
CD_3OD	Deuterated methanol
$CDCl_3$	Deuterated chloroform
CH_3Cl	Chloroform
CILs	Chiral ionic liquids
CLSI	Clinical and laboratory standards institute
CMC	Critical Micelle Concentration
d	Doublet
DCM	Dichloromethane
dd	Double doublet
DMSO-*d*	Deuterated dimethylsulfoxide
DOC	Dissolved organic carbon
dt	Double triplet
g	Gram
H_1	Hexagonal phase
HRMS	High resolution mass spectrometry
hrs	Hours
Hz	Hertz
IL	ionic liquid

IR	Infrared spectroscopy
J	Coupling constant
L	Gel phase
L_1	Micellar solution
L_α	Lamellar
m	Multiple
MBC	minimal bactericidal concentration
mg	Milligram
MIC	Minimal inhibitory concentration
mM	Millimolar
mmol	Millimole
$mN\ m^{-1}$	Millinewton per-meter
mol	Mole
NaOH	Sodium hydroxide
NMR	Nuclear magnetic resonance
OECD	Organisation for Economic Co-operation and Development
PENDANT	Polarizing enhancement nurtured during attached nucleus testing
s	Singlet
SDS	Sodium *n*-dodecyl sulphate
t	Triplet
tert-	Tertiary
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
T_K	Krafft temperature
TLC	Thin layer chromatography
TOC	Total organic carbon

TsCl   Tosyl chloride

(TSILs)   Task-specific ionic liquids

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CHAPTER 1: INTRODUCTION

1.1 A brief history and definition

The most common definition of ionic liquids (ILs) describes them as a class of molten salts with melting points below 100 ℃. The root of ILs stems from the traditional inorganic molten salts which remain in a liquid state at high temperatures. Such molten salts possess some unique characteristics that cannot be provided by traditional molecular solvents. These properties include: 1) inert to thermal and chemical process, 2) possess a wide liquid range and are non-volatile and non-flammable making them good reaction media under strict conditions, 3) high conductivity allows them to play a role in some electrochemical process. However, the high temperature needed to maintain their liquid state (for example, the melting point of NaCl is 801°C) eliminates the practical application of these inorganic molten salts. Efforts have been made to discover new materials with all the mentioned properties but remain at liquid state at lower temperature ranges.

The first observation of ILs was traced back to the 19th century. Red oil was observed in the process of toluene synthesis using a classical Friedel-Craft reaction. The red oil was identified later as a salt called sigma complex (Wilkes, 2002). The first recognized IL, ethyl ammonium nitrate was discovered by Walden (1914). In 1978, Osteryoung and co-workers reported that quaternary pyridinium mixed with aluminium chloride (AlCl$_3$) formed low melting point salts. This discovery was the first report of pyridinium-based ILs (Gale, Gilbert, & Osteryoung, 1978). Imidazolium-based ILs were first reported by Wilkes and co-workers (Fannin *et al.*, 1984; Wilkes, Levisky, Wilson, & Hussey, 1982). The pyridinium- or the imidazolium-based organic salts were blended with AlCl$_3$ in order to synthesize liquid salts at room temperature. However, these binary ILs are air- and moisture-sensitive thereby limiting their practical utility.

The discovery of modern ILs was initiated by Wilkes and Zaworotko (1992) who found that air- and moisture-stable imidazolium-based ILs could be formed by pairing anions that are resistant to hydrolysis, such as BF_4^-, PF_6^-, NO_3^-, SO_4^-, and acetate. This discovery opened a new avenue for the synthesis and application of modern ILs.

Common ILs Cations

imidazolium   pyrrolidinium   pyridinium   ammonium

Common ILs Anions

tetrafluoroborate   hexafluorophosphate   dicyanamide   triflate

bistriflamide
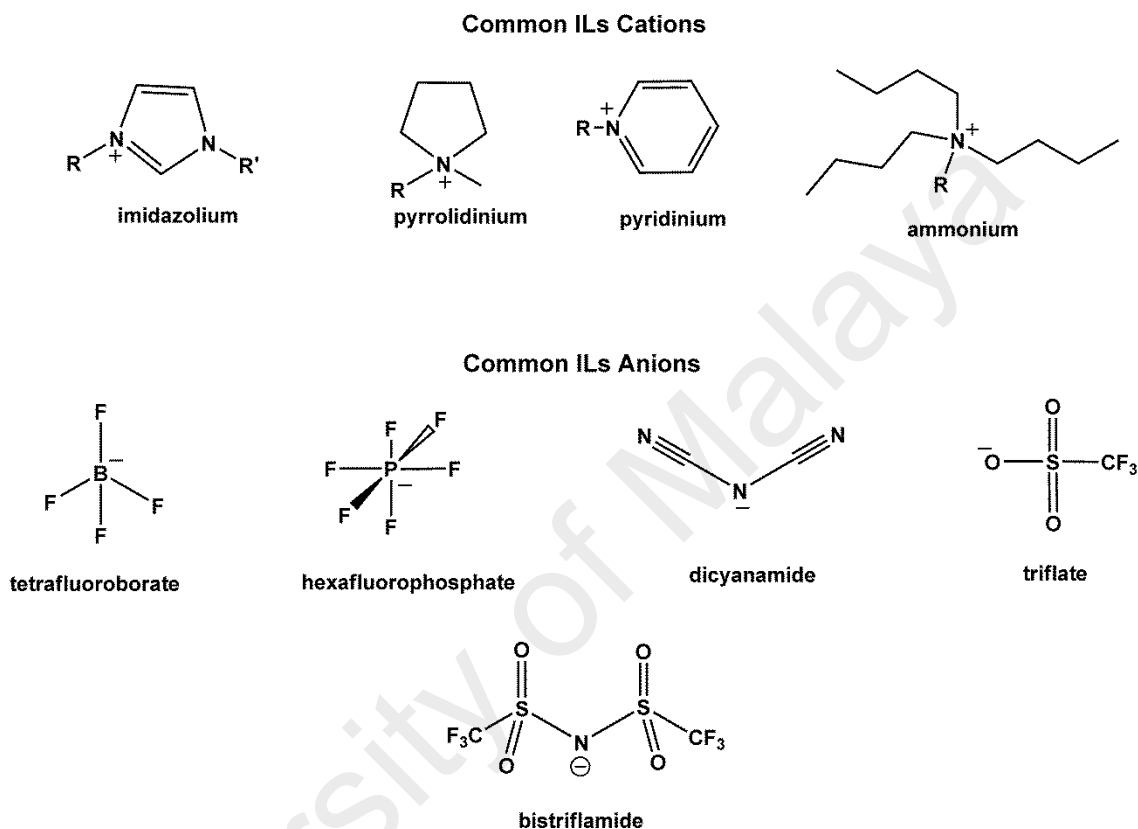
Figure 1.1: Common cations and anions of ILs.

The asymmetric structure and bulky size of the cation or anion are essential for lowering the melting point of ILs (Davis, 2004). The literature shows that the majority of ILs are quaternary ammonium, phosphonium, pyridinium, and imidazolium cations paired with bulky, charge diffusive anions. Figure 1.1 shows typical structures of cations and anions that are often employed for making ILs. Typically, the physical properties of ILs such as viscosity, surface tension, thermal stability, and water solubility are all determined by both the cationic and anionic moieties (Poole, 2004). Generally, [Cl⁻] and [BF_4^-] anion-based ILs are water soluble while [NTf_2^-] and [PF_6^-] anion-based ILs are water-immiscible. For example, 1-butyl-3-methylimidazolium

chloride [bmim][Cl] and 1-butyl-3-methyl imidazolium tetrafluoroborate [bmim] [BF$_4$] are all water soluble (Poole, 2004). However, if the chain length of the alkyl substituents on the imidazolium cation increases, the water solubility of the IL decreases (D. Holbrey & R. Seddon, 1999). For example, 1-octyl-3-methylimidazolium tetrafluoroborate ([Omim][BF$_4$]) is water immiscible.

Moreover, simple modification of traditional ILs by varying their cations and anions can produce ILs with variable and tuneable physicochemical properties that make them much more versatile and useful for a variety of applications (Anderson, Armstrong, & Wei, 2007). Their uses traverse in many areas of chemistry and biochemistry, including novel solvent systems in organic syntheses and catalysis (Cole *et al.*, 2002; Handy & Okello, 2005; Sheldon, 2001; Sheldon, Lau, Sorgedrager, van Rantwijk, & Seddon, 2002; Welton, 1999), enzyme-catalysed reactions (Ebner *et al.*, 2014; Naik, Nara, Harjani, & Salunkhe, 2007; Wahlström, 2014), electrochemical studies (Doyle, Lang, Kim, & Kohl, 2006; Lagrost, Carrié, Vaultier, & Hapiot, 2003; Wang, Mottaghitalab, Too, Spinks, & Wallace, 2007), electrolyte materials for double-layer capacitors, dye-sensitized solar cells, liquid-liquid extractions (Carda–Broch, Berthod, & Armstrong, 2003; Germani, Mancini, Savelli, & Spreti, 2007; Li, Xin, Xu, & Zhang, 2007), additives in HPLC and capillary electrophoresis, and stationary phases in GC (Anderson & Armstrong, 2003; Heintz, Verevkin, & Ondo, 2006; Sumartschenkowa *et al.*, 2006). The tuneable properties include but are not limited to melting point, viscosity, density, thermal stability, hydrophilicity/ lipophilicity and miscibility with water and organic solvents, as well as extractability for various organic compounds and metal ions. Towards improving ILs physicochemical properties, different studies including syntheses of multi-cationic ILs (*i.e.* di-cationic, di-anionic, tri-cationic, tri-anionic, *etc.*), containing different incorporating substitutes into cations, are addressed (Anderson, Ding, Ellern, & Armstrong, 2005; Payagala, Huang, Breitbach, Sharma, & Armstrong,

2007; Pernak, Skrzypczak, Lota, & Frackowiak, 2007; Sharma *et al.*, 2008). These multifunctional ILs (especially di-cationic and di-anionic ILs) revealed a greater range of physical properties than most traditional, mono-cationic ILs. They often have superior thermal stability, lower volatility, and more flexibility in tuning/varying their physiochemical properties. In particular, varying the cationic or anionic moieties to produce symmetrical /unsymmetrical dicationic (or di-anionic) moieties allows greater variety and control of virtually all IL properties. The difficulty in producing multi-cationic ILs in liquid forms (at ambient temperature) associated to the increasing in number of charged groups and their molecular weight. In addition, the synthetic/ manufacturing process can become increasingly complex which raises their production cost. However, in order to improve the chances of large-scale ILs applications, the efficiency of synthetic procedures, IL toxicity and biodegradation have all become important topics. In the present research work synthesis of some new groups of multi-cationic ILs (di, tri and tetra-cationic) is presented using simple and effective methods. In addition, bio-physical and bactericidal properties of these ILs are described herein.

1.2. Research Objectives

The main objective of this research is to synthesis new groups of multi-imidazolium and benzimidazolium based ILs using an effective approach promising maximum yield minimum by-product.

The overall objectives of this research are:

1. To synthesize a group of new multi-cationic ILs from readily available starting materials with high yields and purity.

2. To produce gemini-type based on bis-imidazolium and benzimidazolium ILs.

3. To obtain ILs in liquid forms at ambient temperature.

4. To study molecular modification effect on the biophysical properties of the synthesized ILs.

5. To explore the applications of synthesized ILs in the area of antibacterial, self-assemble behaviour and biodegradable surfactants.

1.3 Thesis layout

To meet the thesis objectives, the study has been prepared to present details on the facts, observations, arguments and procedures where the thesis is organized into seven chapters. Apart from Chapter 1 and 7, each chapter consists of an introduction, relevant literature review, motivation, experimental section, in addition to results and discussion. General background and history of ILs are presented in Chapter 1. Literature review and general synthetic methods of ILs are outlined in Chapter 2 while, the synthesis and characterisation of new imidazole and benzimidazole sulphonamides compounds as well as their antibacterial evaluation against different strains of bacteria addresses in Chapter 3. In Chapter 4, two of these compounds were used as core compounds to synthesis a new series of gemini-type IL based on bis-imidazolium and benzimidazolium using simple method with excellent yield. The effects of different substituted functional groups on the antibacterial activities of imidazolium cation are discussed in this chapter. Same experimental strategy was used to synthesis tri and tetra-cationic ILs as presented in Chapters 5 and 6, respectively, where biodegradable high ordered phase characteristics of both ILs types are presented and discussed in these two chapters. Towards wide medical and industrial applications, these two studies proved the surfactants properties and biodegradability for tris-, tetrakis-imidazolium and benzimid- azolium ILs. Finally, summary of thesis work and recommendations for future studies are presented in Chapter 7. References cited are listed at the end of the thesis followed by several supporting appendices.

CHATER 2: LITERATURE REVIEW

2.1 SYNTHESIS OF IONIC LIQUIDS

Generally the synthesis of the required ILs can be achieved by necessary two steps: first is the formation of the desired cation while the second step represented by the anion exchanging. These two-steps synthesis of ILs are the most widely applied method for ILs preparation, as outlined in Figure 2.1.
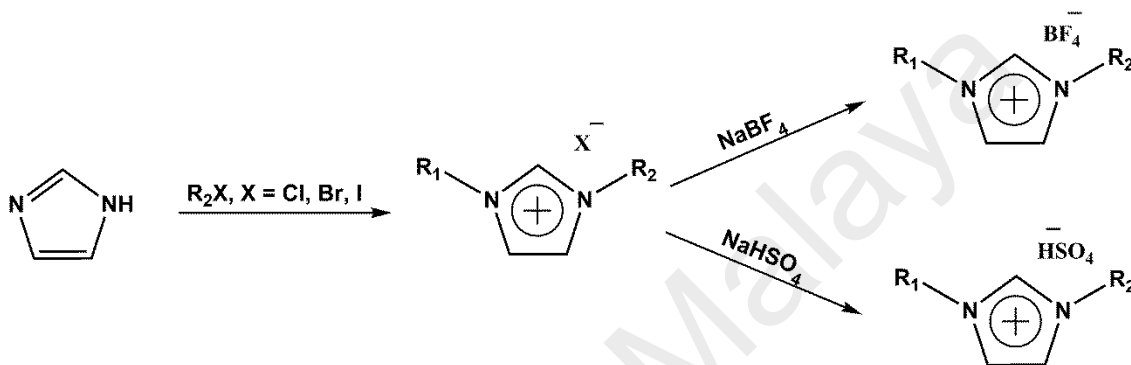
Figure 2.1: Two-step synthesis of ILs

The formation of the cations may be carried out either via protonation with a free acid, or by quaternization of an amine, phosphine or sulfide, most commonly using a halo-alkane or dialkylsulfates. The protonation reaction, as used in the formation of salts such as ethyl-ammonium nitrate, involves the addition of concentrated nitric acid to a cooled aqueous solution of ethylamine. A similar method has been used for the production of low melting, liquid crystalline, long alkyl chain substituted 1-alkylimi-dazolium chloride, nitrate and tetrafluoroborate ILs (Gordon & Muldoon, 2008).

Producing halide ILs by using the alkylation method has many advantages like: the high availability of cheap halo-alkanes and mild conditions are required for these substitution reactions, besides the easy anion-exchanged of the formed halide ILs with other anions. In general, the alkylation of amine can be achieved by using both simple halo-alkanes as well as more complex side chains. The reaction may be carried out using chloro-alkanes, bromo-alkanes and iodo-alkanes, where the reactivity of substitution reaction in the order $Cl < Br < I$, as is expected for nucleophilic substitution

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reactions. Fluoride salts cannot be formed in this manner. According to reactivity of halo-alkanes, the reaction conditions (*i.e.* temperature and time) are dependent on the used alkylating agent, where chloro-alkanes being the least reactive and iodo-alkanes the most. Further, the reactivity decreases with increasing alkyl chain length. For example; it is necessary to heat the mixture of 1-methylimidazole with chloro-alkanes to about 80 °C for 2–3 days to ensure complete reaction. The equivalent reaction with bromo-alkanes is usually complete within 24 h, and can be achieved using lower temperatures (50–60 °C). In the case of bromo-alkanes, significant increasing in the reaction rate was noticed with discoloration of the final product (Gordon & Muldoon, 2008).

Theoretically, the quaternization reactions are extremely simple which includes stirring of amine (or phosphine) with the desired alkylating agent at reasonable temperature. Similar techniques are used for other amines like; pyridine (Gordon, Holbrey, Kennedy, & Seddon, 1998), 1-methylpyrrolidine (MacFarlane, Meakin, Sun, Amini, & Forsyth, 1999), and trialkylamines (Sun, Forsyth, & MacFarlane, 1998). As the most of the produced ILs are extremely hygroscopic, the important requirement is keeping the reaction mixture free of moisture where the reaction has to be carried out under nitrogen or some other inert gas in order to exclude water and oxygen during the quaternization. Generally, the reaction may be achieved in pure form (*i.e.* without using a solvent), as the reagents are liquids and mutually miscible, while the halide IL products are usually immiscible in the starting materials. This feature is providing beneficial advantages in separating IL with suitable purity and yield.

The high immiscibility of halide IL product with the starting material reagents plays a major role in the synthesis of halide ILs via either solvent-free reaction or in the presence of solvent, which is formed as a separate phase. The removal of the excess solvent and starting material can be achieved by simply decantation which considered as

a practical advantage of the solvent using. Moreover, Gro and Jess (2005) presented a detailed study of the solvent's effect by comparing the kinetics of a single-phase reaction to those of a biphasic system in the synthesis of [bmim]Cl. In all cases, after reaction is complete and the solvent is decanted, it is necessary to remove all excess solvent and starting material by heating the IL under reduced pressure. Care should be taken at this stage, especially in the case of halide ILs, as overheating can result in a reversal of the quaternization reaction. It is not advised to heat the halide salts to temperatures greater than about 80 °C.

Typically, the most common starting materials are 1-alkylimidazole which are readily available and provides access to a great number of cations likely to be of interest to most researchers. There is only a limited range of other *N*-substituted imidazoles commercially available and many are relatively expensive.

2.1.1 Alkylation of imidazoles

The alkylation of alkyl or aryl imidazoles in variety of solvents is the key step in synthesis of ILs based imidazoles. While the commercially available sources of alkyl or aryl imidazoles are limited. Therefore, the synthesis of the new alkyl imidazoles is extremely useful to obtain plenty of ILs derivatives. Subsequently, treatment of imidazoles with alkyl halides under basic conditions affords alkyl imidazoles in high purity with simple extraction. Numerous alkyl halides could be applied to get ILs in good yield. The removal of remaining starting materials from the reaction mixture is a serious problem. Several techniques were used to overcome these problems. However, the purification methods would add significant costs on the production. On the other hand, the methodology which consumes of most of the starting materials in relatively short time is preferable. Thus, the most reactive alkyl halides are the best choice, such as alpha-methylene derivatives. The synthesis of 1-alkylimidazoles may be achieved without great difficulty, as indicated in Figure 2.2.
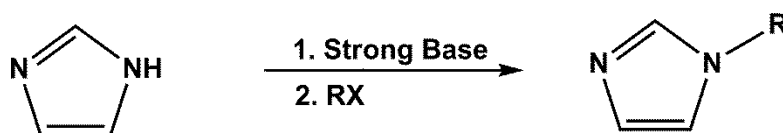
Figure 2.2: Synthesis of 1-alkylimidazoles.

Varieties of C-substituted imidazoles are commercially available which can be easily used to obtain many different alkylimidazoles as starting materials (Figure 2.2). The combination of these substituted alkylimidazoles can further be used for the synthesis of variably substituted ILs.

2.1.2 Anion-exchange Reactions

The main goal of all anion-exchange reactions is production of the desired IL uncontaminated with unwanted cations or anions, a task that is easier for water immiscible ILs. Anion metathesis is the most used approach in both water-miscible and -immiscible ILs types.

2.1.3 Metathesis of anion

The first preparation of air- and water-stable ILs based on 1,3-dialkyl-methyl-imidazolium cations (sometimes referred to as "second generation" ILs) was reported by Wilkes and Zaworotko (1992). This preparation involved a metathesis reaction between [C$_2$mim]I and a range of silver salts (Ag[NO$_3$], Ag[NO$_2$], Ag[BF$_4$], Ag[CH$_3$CO$_2$], and Ag[SO$_4$]) in methanol or aqueous methanol solution. After simple filtration of silver iodide as a sparingly soluble salt in these solvents and removal of the reaction solvent, ILs would isolate in good yield and purity. This method remains the most efficient for the synthesis of water-miscible ILs, but is obviously limited by the relatively high cost of silver salts, not to mention the large quantities of solid by-product produced.

The first report of a water-insoluble IL was two years later, with the preparation of [C$_2$mim][PF$_6$] from the reaction of [C$_2$mim]Cl and HPF$_6$ in aqueous solution (Fuller,

Carlin, De Long, & Haworth, 1994). The procedures that described in the above two papers have stood the test of time, although many subsequently suggested refinements of the used approaches. Most notably, many ILs of the $[C_2mim]^+$ cation are solid at ambient temperature, subsequently their purification may be achieved via recrystallization. Because of the producing ILs in liquid form at room temperature is preferable in many applications, most researchers currently employ cations with 1-alkyl substituents of chain length 4 or greater, which results in a considerable lowering in melting point. However, an enormous variety of anion exchange reactions has been recently reported for the preparation of ILs. Table 2.1 elucidates a representative selection of both commonly used and more esoteric example of anions source.

Table 2.1: Examples of ILs prepared by anion metathesis (Gordon & Muldoon, 2008).

IL	Anion source
[cation][PF_6]	HPF_6
[cation][BF_4]	HBF_4, NH_4BF_4, $NaBF_4$
[cation][$(CF_3SO_2)_2N$]	$Li[(CF_3SO_2)_2N]$
[cation][CF_3SO_2]	$CF_3SO_2CH_3$, $NH_4[(CF_3SO_2)]$
[cation][CH_3CO_2]	$Ag[CH_3CO_2]$
[cation][CF_3CO_2]	$Ag[CF_3CO_2]$
[cation][$CF_3(CF_2)_3CO_2$]	$K[CF_3(CF_2)_3CO_2]$
[cation][NO_3]	$AgNO_3$, $NaNO_3$
[cation][$N(CN)_2$]	$Ag[N(CN)_2]$
[cation][$CB_{11}H_{12}$]	$Ag[CB_{11}H_{12}]$
[cation][$AuCl_4$]	$HAuCl_4$

The solubility of the ILs in water depends on both anion and cation type, and generally it will decrease by increasing the organic character of the cation. The water-

immiscible ILs could be prepared through considering an aqueous solution of a halide salt of the desired cation as the first step in the preparation process. The cation exchange is then carried out using either the free acid of the appropriate anion, or a metal or ammonium salt. Where available, the free acid is probably to be favored, as it leaves only HCl, HBr or HI as the by-product, easily removed from the final product by washing with water. It is recommended that these reactions are carried out with cooling of the halide salt in an ice bath, as the addition of a strong acid to an aqueous solution is often exothermic. In cases where the free acid is unavailable, or inconvenient to use, however, alkali metal or ammonium salts may be substituted without major problems. It may also be preferable to avoid using the free acid in systems where the presence of traces of acid may cause problems. A number of authors have outlined broadly similar methods for the preparation of $[PF_6]^-$ and $[(CF_3SO_2)_2N]^-$ salts that may be adapted for most purposes (Bonhôte, Dias, Papageorgiou, Kalyanasundaram, & Grätzel, 1996; Huddleston, Willauer, Swatloski, Visser, & Rogers, 1998).

The preparation of water-miscible ILs can be a more demanding process, as the separation of the desired and undesired salts may be complex. The use of silver salts (described above) allows the preparation of many salts in high purity, but is clearly too expensive for large-scale use. As a result, a number of alternative protocols have been developed that employ cheaper salts for the metathesis reaction. The most common approach remains to carry out the exchange in aqueous solution using either the free acid of the appropriate anion, the ammonium salt, or an alkali metal salt. When using this approach, it is important that the desired IL can be isolated without excess contamination from unwanted halide-containing by-products. A reasonable compromise has been suggested by Lancaster, Welton, and Young (2001) for the preparation of [bmim][BF$_4$]. In this approach, which could in principle be adapted to many other water-miscible systems, the IL is formed by metathesis between [bmim]Cl and HBF$_4$ in

aqueous solution. The product is extracted into CH_2Cl_2, and the organic phase is then washed with successive small portions of deionized water until the washings are pH neutral. The presence of halide ions in the washing solutions can be detected by testing with $AgNO_3$. The CH_2Cl_2 is then removed on a rotary evaporator and the IL purified further by mixing with activated charcoal for 12 h. Finally, the liquid is filtered through a short column of acidic or neutral alumina and dried by heating in vacuo. Yields of around 70% are reported when this approach is carried out on large ($\sim$1 molar) scale. Although the water wash can result in a lowering of the yield, the aqueous wash solutions may ultimately be collected together, the water removed, and the crude salt added to the next batch of prepared IL. In this manner, the amount of product loss is minimized, and the purity of the prepared IL appears to be reasonable for most applications.

Alternatively, the metathesis reaction may be carried out entirely in an organic solvent such as CH_2Cl_2 (Cammarata, Kazarian, Salter, & Welton, 2001), or acetone (Fuller & Carlin, 1998). In both of these systems, the starting materials are not fully soluble in the reaction solvent, so the reaction is carried out as a suspension. In the case of the CH_2Cl_2, the reaction was carried out by stirring the 1-alkyl-3-methylimidazolium halide salt with the desired metal salt at room temperature for 24 h. The insoluble halide by-products were then removed by filtration. Although the halide by-products have limited solubility in CH_2Cl_2, they are much more soluble in the IL/ CH_2Cl_2 mixture. Thus, when this method is employed, it is important that the CH_2Cl_2 extracts are washed with water to minimize the halide content of the final product. This process was reported to give final yields in the region of 70–80%, and was used to prepare ILs containing a wide variety of anions ($[PF_6]^-$, ($[BF_4]^-$, $[ClO_4]^-$, $[CF_3SO_3]^-$, $[NO_3]^-$, and $[CF_3CO_2]^-$). In the case of the acetone route, $[C_2mim]Cl$ was stirred with $[NH_4][BF_4]$ or $[NH_4][CF_3SO_3]$ at room temperature for 72 h. The insoluble $[NH_4]Cl$ by-product was

removed by filtration and no water wash was carried out. The trace organic impurities were removed by stirring the acetone solution with neutral alumina for 2 h. Purities of at least 99.95% were obtained after removal of the metal halide salts by filtration.

2.1.4 Purification of Ionic Liquids

In principle, the lack of significant vapour pressure prevents the purification of ILs by distillation, thus any volatile impurity can be separated from an IL by distillation. In general, it is better to remove as many impurities as possible from the starting materials and, where possible, to use synthetic methods that either generates as few side products as possible, or allow their easy separation from the final IL product. The first requirement is that all starting materials used for the preparation of the cation should be distilled prior to use. In addition, all the solvents used in quaternization or anion-exchange reactions should also be dried and distilled before use. Purification of ILs formed by anion metathesis can throw up a different set of problems. In this case, the most common impurities are halide anions, or unwanted cations inefficiently separated from the final product. The presence of such impurities can be extremely detrimental to the performance of the ILs.

In general, there is much more problems in water-miscible ILs comparing to the water-immiscible ILs which can be purified efficiently by washing with water. The problems inherent in the preparation of water-miscible salts have been highlighted by Seddon, Stark, and Torres (2000), who studied the Na^+ and Cl^- concentrations in a range of ILs formed by the reaction of [emim]Cl and [bmim]Cl with $Ag[BF_4]$, $Na[BF_4]$, $Ag[NO_3]$, and HNO_3. They found that the physical properties such as density and viscosity of the liquids can be radically altered by the presence of unwanted ions. The results showed that all the preparations using Na^+ salts resulted in high residual concentrations of Cl^-, while the use of Ag^+ salts gave rise to much lower levels. The low solubility of NaCl in the ILs indicates that the impurities arise because the reaction

does not proceed to completion with the Na^+ salts. Indeed, it was reported that unreacted [bmim]Cl was isolated by crystallization from [bmim][NO$_3$] in one case.

Most ILs based on the common cations and anions should be colourless, with minimal absorbance at wavelengths >300 nm. In practice, the ILs often take on a yellow colour, particularly during the quaternization step. The amount of impurity causing this is generally extremely small, being undetectable using ^{1}H-NMR and CHN microanalysis, and in many applications the discoloration may not be of any importance. Up to date, the precise origin of these impurities has not been determined, but it seems likely that they arise from unwanted side reactions involving oligo-merization or polymerization of small amounts of free amine, or else from impurities in the starting materials. However, it is important that the ILs are colourless where the colour may be minimized by following a few general steps:

(i) all starting materials should be purified (Armarego & Chai, 2009),

(ii) The presence of traces of acetone can sometimes result in discoloration during the quaternization step. Thus, all glassware used in this step should be kept free from this solvent.

(iii) The quaternization reaction should be carried out either in a system that has been degassed and sealed under nitrogen, or else under a flow of inert gas such as nitrogen. Furthermore the reaction temperature should be kept as low as possible (no more than 80 °C for Cl$^-$ salts, and lower for Br$^-$ and I$^-$ salts).

If the ILs remain discolored even after these precautions, it is often possible to further purify them by first stirring with activated charcoal, and then passing the liquid down a short column of neutral or acidic alumina (Cammarata *et al.*, 2001). Clearly, the impurity likely to be present in largest concentrations in most ILs is water. The removal of other reaction solvents is generally easily achieved by heating the IL under vacuum. Water is generally one of the most problematic solvents to remove, and it is generally

recommended that ILs are heated to at least 70° C for several hours with stirring to achieve an acceptably low degree of water contamination. Even water-immiscible salts such as [bmim][PF$_6$] can absorb water when exposed to the air (Cammarata *et al.*, 2001; Tran, De Paoli Lacerda, & Oliveira, 2003). Thus, it is advised that all ILs are dried directly before use.

2.1.5 Task-specific Ionic Liquids

Task-specific ionic liquids (TSILs) may be defined as ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the IL. Further, the incorporation of this functionality should imbue the salt with a capacity to behave not only as a reaction medium but also as a reagent or catalyst in some reactions or processes. The definition of TSIL also extends to "conventional" ILs to which ionic solutes are added to introduce a functional group into the liquid. Logically, when added to a "conventional" IL, these solutes become integral elements of the overall "ion soup" and must then be regarded as an element of the IL as a whole, making the resulting material a TSIL. Conceptually, the functionalized ion of a TSIL can be regarded as possessing two elements. The first is a core that bears the ionic charge and serves as the locus for the second element; the substituent group. Established TSILs are largely species in which the functional group is cation-tethered. Consequently, the synthesis of TSIL will mainly stress the synthesis of salts possessing functionalized cations and anions as well.

2.1.6 General Synthetic Strategies of Task-specific Ionic Liquids

The incorporation of functionality into an ion intended for use in formulating an IL is usually a multi-step process. Consequently, a number of issues must be considered in planning the synthesis of the ion, where the first of these is the choice of the cationic core. The core of TSIL cations may be as a simple single atom such as N, P or S, that found in ammonium, phosphonium or sulphonium ions, respectively, or the core of the

ion may be (and frequently is) a heterocycle such as imidazole or pyridine. The choices made in this regard will play a large role in both the chemical and physical properties of the resulting IL. For example, ILs incorporating phosphonium cations generally exhibit the greatest thermal stability, but also commonly possess higher melting points than salts of other cations (Karodia, Guise, Newlands, & Andersen, 1998). Thus, if the desired IL is to be used in a process that is conducted at 0 °C, building the cation core around a phosphonium ion may prove especially challenging. If the IL is to be used in a metal catalysed reaction, the use of an imidazolium-based IL might be critical, especially in the light of the possible involvement in some reactions of imidazolylidene carbenes originating with the IL solvent (Mathews, Smith, Welton, White, & Williams, 2001).

The second element of general importance in the synthesis of a task-specific IL is the source of the functional group that is to be incorporated. Key to success here is the identification of a substrate that contains two functional groups with different reactivity, one which allows the attachment of the substrate to the core, and the other which either is the functional group of interest or is modifiable to the group of interest. Functionalized alkyl halides are commonly used in this capacity, also the triflate- esters of functionalized alcohols work as well (Davis & Wasserscheid, 2008; Fei, Geldbach, Zhao, & Dyson, 2006). Moreover, the choice of reaction solvent is also of concern in the synthesis of new TSIL. Toluene and acetonitrile are the most widely used solvents, the choice in any given synthesis being dictated by the relative solubility of the starting materials and products.

In the case of the TSIL carrying a functionalized cation, the choice of the anion that is to ultimately be an element of the IL is of particular importance. Perhaps more than any other single factor, it appears that the anion of the IL exercises a significant degree of control over the molecular solvents (water, ether, *etc.*) with which the IL will form

two-phase systems. For example, nitrate salts are typically water miscible and those of hexafluorophosphate are not; those of tetrafluoroborate may or may not be, depending on the nature of the cation. Certain anions such as hexafluorophosphate are subject to hydrolysis at higher temperatures, while those such as bis(trifluoromethyl-sulphonyl)amide are not, but are significantly more expensive. Additionally, the cation of the salt used to perform any anion metathesis is important. While salts of potassium, sodium and silver are routinely used for this purpose, the use of ammonium salts in acetone is frequently the most convenient and least expensive approach. Although the first IL expressly categorized as being "task-specific" featured the incorporation of function within the cation core, subsequent research has focused on the incorporation of functionality into a branch appended to the cation, especially imidazolium cation (Lee, 2006); Figure 2.3.

Functionalized imidazolium salts for task-specific ionic liquids
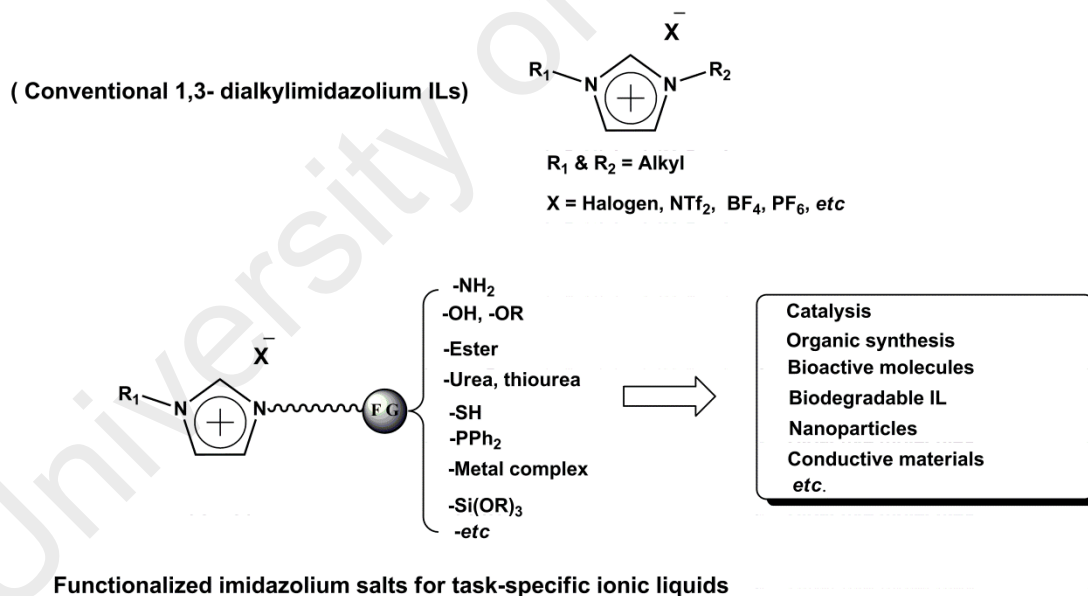
Figure 2.3: Imidazolium salts for conventional ILs and functionalized imidazolium salts for TSIL.

In this fashion, a great number of the task-specific ILs have been prepared by quaternization of the aforementioned alkyl-imidazoles with a functionalized alkyl halide to afford the corresponding functionalized imidazolium halides in usually good yield (Figure 2.4). The preparation of functionalized pyridinium, phosphonium, *etc*. cations

may be accomplished in similar approach. Recent advances in ILs research has provided routes for achieving functionalized ILs in which a functional group is covalently tethered to the cation or anion of the IL, especially to the two *N* atoms of the imidazole ring. It is expected that these functionalized ILs may further enlarge the application scope of ILs in chemistry. In addition to TSILs with either functionalized cations or functionalized anions, the first examples of "dual-functionalized ionic liquids" (DF-IL) in which both cation and anion contain functionalities have also been reported by Zhao, Fei, Ohlin, Laurenczy, and Dyson (2004).

R = CH₂, *n*-C₄H₉
R' = Functional group
X = Halogen
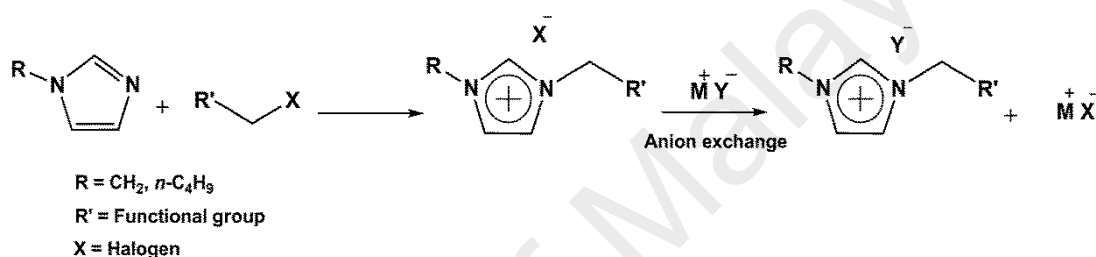
Figure 2.4: General synthesis of Task Specific Ionic Liquids with functionalized cations from 1-alkylimidazoles.

2.2 MULTI-CATIONIC IONIC LIQUIDS

On the basis of the cation, ILs may be divided into five groups: (1) five-membered heterocyclic cations, (2) six-membered and benzo-fused heterocyclic cations, (3) ammonium, phosphonium and sulphonium based cations, (4) functionalized imidazolium cations and (5) chiral cations. Generally, through modification of the cation, the properties of the ILs, notably the melting point and liquid range (Davis, 2004; Welton, 1999), viscosity (Bonhôte *et al.*, 1996; Sánchez, Espel, Onink, Meindersma, & Haan, 2009; Tokuda *et al.*, 2006) and miscibility with other solvents (Handy, 2003; Huddleston *et al.*, 1998), can be altered.

Moreover, ILs can be classified according to the number of cations (or anions) that are shared in the formation of IL *e.g.* di-cationic, di-anionic, tri-cationic, tri-anionic, *etc*. Multi-cationic ILs (especially di-cationic and di-anionic ILs) and their properties can be "tuned", controlled or altered to a greater extent than more conventional ILs. In fact,

dicationic ILs have advantage over monocationic ILs represented by providing further fine tuning opportunities to their physical and chemical properties. Each structure contains two cationic moieties and two anionic moieties that can be varied with respect to each other. Precisely, varying the cationic or anionic moieties to produce symmetrical /unsymmetrical dicationic moieties allows greater variety and control of virtually all IL properties (Payagala *et al.*, 2007).

Geminal dicationic ILs are new class of amphiphilic molecules containing two head groups contain two identical or dissimilar cationic moieties and two aliphatic chains, linked by a rigid or flexible spacer. They showed superior physical properties compared to single charged ILs (Ding, Zha, Zhang, & Wang, 2007a; Payagala *et al.*, 2007; Shirota, Mandai, Fukazawa, & Kato, 2011). However, they possess the same desirable solvation properties as the more common singly charged ILs (Anderson, Ding, Welton, & Armstrong, 2002). They are able to dissolve all manner of polar and non-polar molecules including some proteins, peptides, polymers and simple organic molecules. In some instances geminal dicationic ILs exhibited higher melting points than their monocationic analogues, sometimes even extending beyond the accepted IL region of 100 $^{\circ}$C (Rogers & Seddon, 2003). The most common methodology applied to lower the melting point is changing the counter anion. But this alters the solvation properties of the IL, and even in cases where optimal anions (*e.g.* NTf_2^-, PF_6^-, BF_4^-, *etc.*) are used, some dicationic salts remained solids. More detailed reviews studies related synthesis of symmetrical and unsymmetrical dicationic ILs are explained in Chapter 4, Section 4.1.

The rigid geometry and the existence of multi-charged moieties in the close proximity resulted with high apparent polarity and relatively high melting salts. Based on these observations, it was concluded that for multi-cationic ILs, the linear geometry would give the best tenability in terms of physicochemical properties and the highest probability of solvation ILs. However, good thermal stabilities of tri-cationic ILs with

their tested antimicrobial activities results are reported (Pernak *et al.*, 2007). Unsymmetrical moieties prepared by reacting (1,2,3-tri(chloromethoxy)-propane) with alkyl-imidazoles and alkyl-pyridines, were used to synthesize these tri-cationic ILs (see Figure 2.7 in Section 2.3). Further, Sharma *et al.* (2008) have revealed the effect of molecular structure modifications on the physicochemical properties of 28 new symmetrical tri-cationic ILs series. They observed that the physicochemical properties of tri-cationic ILs often can be varied and controlled to a greater extent than conventional mono-cationic ILs. The melting point of tri-cationic ILs are depending on the flexibility of the central core system; for example, ILs (Core D) with more flexible structure have low melting points as compared to ILs (Core A) having more rigid structures (Figure 2.5). However, they found that the solubility of these tri-cationic ILs in water and heptane appears very similar to that of the traditional monocationic and dicationic ILs and depends largely on the selected anion.

Tricationic core moieties

R groups
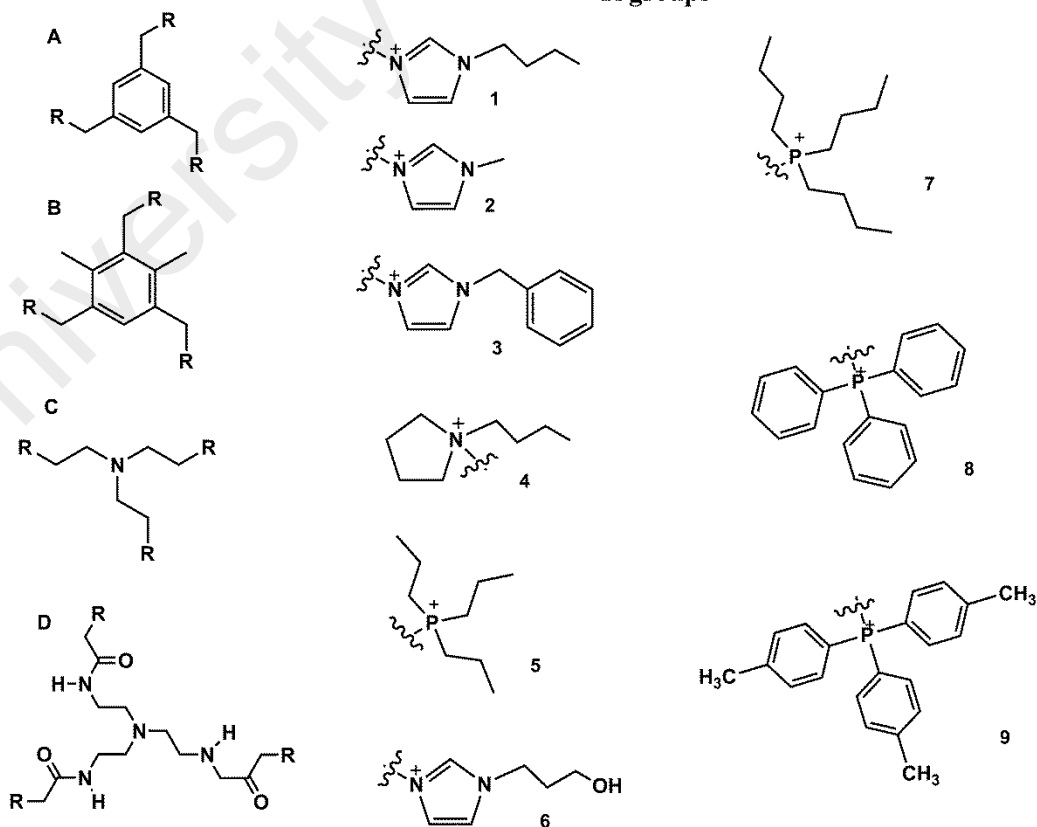
Figure 2.5: Structures of symmetrical tri-cationic ILs presented and examined by Sharma *et al.* (2008).

2.3 BIOLOGICAL ACTIVITY OF ILS

ILs are providing broad applications at the interface of chemistry with the life sciences, *e.g.* acting as solvents in enzymatic (van Rantwijk & Sheldon, 2007) and whole-cell biocatalysis (Bräutigam, Bringer-Meyer, & Weuster-Botz, 2007; Pfruender, Jones, & Weuster-Botz, 2006), and as protein stabilisation agents (Byrne, Wang, Belieres, & Angell, 2007; Fujita, MacFarlane, & Forsyth, 2005; Vrikkis, Fraser, Fujita, MacFarlane, & Elliott, 2009). Moreover, due to their potential use as active pharmaceutical ingredients, they gained further highlights in biochemical studies (Bica, Rijksen, Nieuwenhuyzen, & Rogers, 2010; Hough & Rogers, 2007; Hough *et al.*, 2007; Stoimenovski, MacFarlane, Bica, & Rogers, 2010).

The experimental data available in different studies revealed that ILs exhibited distinct mechanisms toward cell membrane such as binding, insertion, and disruption behaviours that could be correlated with their biological activities (Gal *et al.*, 2012; Gal *et al.*, 2013; Petkovic, Seddon, Rebelo, & Silva Pereira, 2011; Wang, Wei, Wang, Sun, & Wang, 2015). The results indicate, in particular, that both the side chain composition and particularly the head-groups of ILs constitute determinants for membrane activity and consequent cell toxicity.

There are continuous attempts to understand the mechanisms of ILs toxicity and their biological impact due to the existence of some critical questions, yet unresolved, such as their modes of toxicity, biodegradation pathways, and behaviour concerning bio-sorption. Generally, major biological impact of ILs can be attributed to their interactions with cellular membrane. The disruption of the plasma membrane plays a major role in IL toxicity where most toxicology studies have correlated the lipophilicity of IL ion-pairs with their biological effects (Matzke, Stolte, Arning, Uebers, & Filser, 2008; Stolte *et al.*, 2007). Moreover, due to high structural similarity between ILs and cationic

surfactants, several ILs act as surfactants which are generally highly disruptive to membranes (Bernot, Kennedy, & Lamberti, 2005) (further details related to surfactants toxicity can be found in Section 2.9). Another suggested mechanism of toxicity and antimicrobial activity is through inhibition of the enzyme acetylcholinesterase. It was illustrated in studies of the inhibitory effects of imidazolium and pyridinium ILs which were shown to inhibit purified enzyme with EC50 levels as low as 13 µM (Stock *et al.*, 2004).

Previous studies have correlated the toxicity of ILs with increasing alkyl chain length of the cationic constituent. These studies proposed that the alkyl chains insert through the polar head-group region of the membrane bilayer, and consequently induce membrane damage and cell death (Evans, 2006; Schaffran, Justus, Elfert, Chen, & Gabel, 2009). Although many research works concentrated on the mi-cellar properties and biological effects of ILs having long alkyl chains (Anderson, Pino, Hagberg, Sheares, & Armstrong, 2003), little is known about the behaviour of ILs with short side residues or ILs exhibiting side-chains bearing oxygen atoms especially their putative membrane interactions. The presence of an oxygenated side chain on the cation appeared to improve the ILs biological effects at different cellular levels.

Many of the recent studies have demonstrated that ILs exhibited excellent antimicrobial activity with a potential application as biocidal agents in the control of microorganisms and infection effects. Early examinations have shown quaternary ammonium (QA) imidazolium and pyridinium compounds to have significant toxic effects on a variety of bacteria and fungi (Pernak, Rogoża, & Mirska, 2001; Shao, Jiang, Meng, & Qing, 2003). Ecotoxicological studies on several ILs have revealed that imidazolium and pyridinium ILs exhibit significant toxicity towards the freshwater algae *Pseudokirchneriella subcapitata* (Pham, Cho, Min, & Yun, 2008), while imidazolium ILs are toxic to the freshwater crustacean *Daphnia magna* (Wells &

Coombe, 2006) and *Caenorhabditis elegans* (Swatloski *et al.*, 2004). The antimicrobial activities of five new groups of choline-like quaternary ammonium chloride ILs were evaluated against a range of Gram positive and Gram negative bacteria (Pernak & Chwała, 2003). All tested ILs displayed significant level of antimicrobial activity where substituent cations of 12 carbon atoms in the alkyl chain exhibited the highest antimicrobial activity against the range tested of microorganisms. Similar trend was shown in alkoxy substituents of twelve carbon atoms to imidazolium ILs against the tested bacteria and fungi (Pernak, Goc, & Mirska, 2004). Further study of dialkloxymethyl substituted of imidazolium ILs $[(C_nO_m)_2im][X]$ (Figure 2.6) by Pernak, Sobaszkiewicz, and Foksowicz-Flaczyk (2004) also revealed broad-spectrum antimicrobial activity towards various bacterial rods, cocci and fungi.

$R = C_3H_7 \quad R = C_4H_9$
$R = C_5H_{11} \quad R = C_6H_{13}$
$R = C_7H_{15} \quad R = C_8H_{17} \qquad X = \bar{Cl}, \bar{BF_4}, \bar{NTf_2}$
$R = C_9H_{19} \quad R = C_{10}H_{21}$
$R = C_{11}H_{23} \quad R = C_{12}H_{25}$
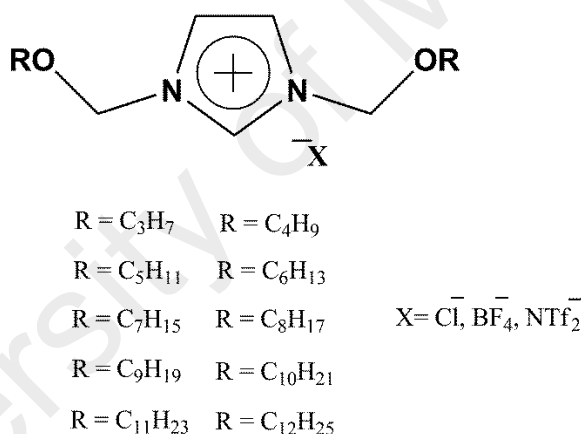
Figure 2.6: Series of $[(C_nO_m)_2im][X]$ ILs prepared by Pernak, Sobaszkiewicz, *et al.* (2004).

Two series of trigeminal tri-cationic imidazolium (**1**) or pyridinium (**2**) chlorides (Figure 2.7) were prepared and their antimicrobial activity was evaluated by Pernak *et al.* (2007). Chloride IL of imidazolium trigeminal tri-cationic with octyl substituent showed the highest bio-effectiveness against rods, cocci, bacilli, and fungi. The obtained results revealed that the prepared tri-cationic ILs have a broad spectrum of antimicrobial activity, as well as the chloride ILs are much more effective than commercially available benzalkonium chloride.
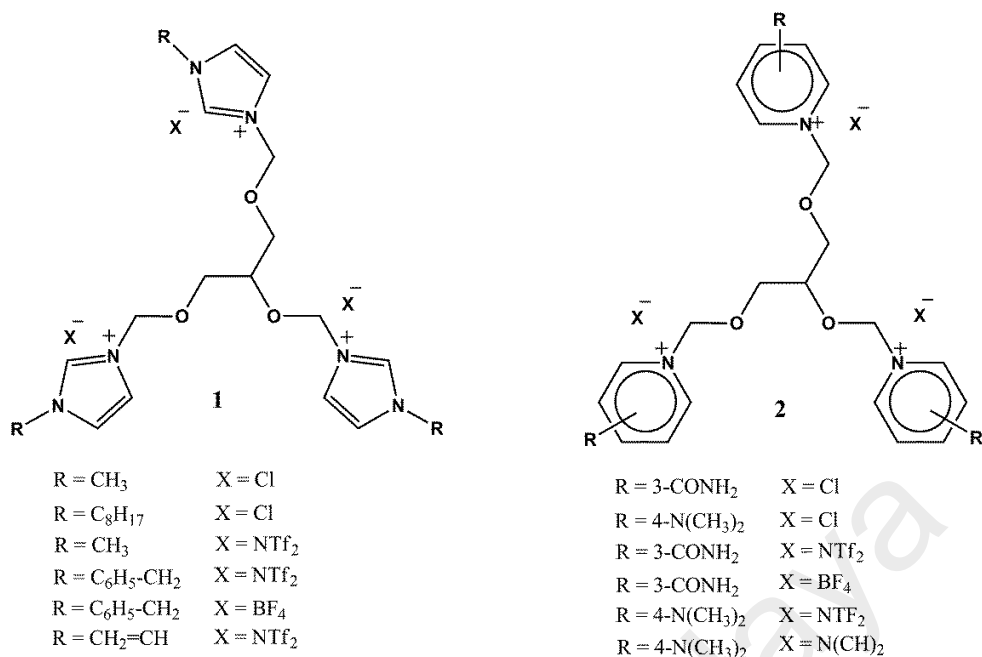
Figure 2.7: Trigeminal tri-cationic imidazolium **(1)** and pyridinium **(2)** ILs by Pernak *et al.* (2007).

Antimicrobial toxicity studies incorporating drug resistant bacterial and fungal strains have been achieved by Coleman, Spulak, Garcia, and Gathergood (2012). These studies allowed for simultaneous screening of toxicity in the environment and medicinal properties of the synthesised chiral ILs (CILs) (Figure 2.8). A medicinal 'hit' was observed against an antibiotic resistant strain of Methicillin-resistant *Staphylococcus aureus* (MRSA).

Left structure labels:

R = CH$_2$-(C$_6$H$_5$), R$_1$ = C$_2$H$_5$
R = CH$_2$-(C$_6$H$_5$), R$_1$ = C$_4$H$_9$
R = CH(CH$_3$)$_2$, R$_1$ = CH$_3$
R = CH(CH$_3$)$_2$, R$_1$ = C$_2$H$_5$
R = CH(CH$_3$)$_2$, R$_1$ = C$_4$H$_9$
R = CH$_3$, R$_1$ = C$_2$H$_5$
R = CH(CH$_3$)CH$_2$CH$_3$, R$_1$ = C$_4$H$_9$
R = CH(CH$_3$)$_2$, R$_1$ = CH$_3$
R = CH(CH$_3$)$_2$, R$_1$ = C$_2$H$_5$
R = CH$_2$-(C$_6$H$_5$), R$_1$ = CH$_3$
R = CH$_2$-(C$_6$H$_5$), R$_1$ = C$_2$H$_5$

Right structure labels:

R = CH$_3$, R$_1$ = CH(CH$_3$)$_2$, R$_2$ = CH$_3$
R = CH$_3$, R$_1$ = CH$_2$(C$_6$H$_5$), R$_2$ = C$_2$H$_5$
R = CH(CH$_3$)$_2$, R$_1$ = CH$_3$, R$_2$ = C$_2$H$_5$
R = CH(CH$_3$)$_2$, R$_1$ = CH$_2$(C$_6$H$_5$), R$_2$ = C$_2$H$_5$
R = CH$_2$-(C$_6$H$_5$), R$_1$ = CH(CH$_3$)$_2$, R$_2$ = C$_2$H$_5$
R = CH$_2$-(C$_6$H$_5$), R$_1$ = CH$_2$CH(CH$_3$)$_2$, R$_2$ = CH$_3$
R = CH$_2$-(C$_6$H$_5$), R$_1$ = CH$_3$, R$_2$ = CH$_3$
R = CH$_2$-(C$_6$H$_5$), R$_1$ = CH$_2$-(C$_6$H$_5$), R$_2$ = C$_2$H$_5$

Figure 2.8: General structures of amino acid and dipeptidyl based chiral ILs (CILs) presented by Coleman *et al.* (2012).

Recently, Garcia, Ribosa, Perez, Manresa, and Comelles (2014) studied the antimicrobial activity besides to thermal stability and self-assembly behaviour of two series of imidazolium and pyridinium ILs. These ILs containing an amide functional group in the hydrophobic side chain are attached to the polar head, 1-alkylcarbamylmethyl-3-methylimidazolium bromides and 1-alkylcarbamylmethylpyrid-inium bromides (Figure 2.9). Moreover, the effect of incorporating a strong hydrogen bonding functionality on aggregation behaviour and antimicrobial activity were investigated. Mester, Wagner, and Rossmanith (2015) addressed the antimicrobial effects of short chained imidazolium-based ILs towards two model microorganisms with a focus on the chaotropicity of the anion. In this study, biological activities of each IL were determined in terms of minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC) against Gram-positive *Listeria monocytogenes* and Gram-negative *Escherichia coli*. In addition to the MIC and MBC, the short-term induced (30 min) toxicity was also studied, to compare the results of the toxicity tests with previous studies, which investigated the effect of similar ILs on protein levels.

C_nAmimBr   C_nApyrBr

C_6AmimBr   C_6ApyrBr

C_8AmimBr   C_8ApyrBr

C_10AmimBr   C_10ApyrBr

C_12AmimBr   C_12ApyrBr

C_14AmimBr   C_14ApyrBr
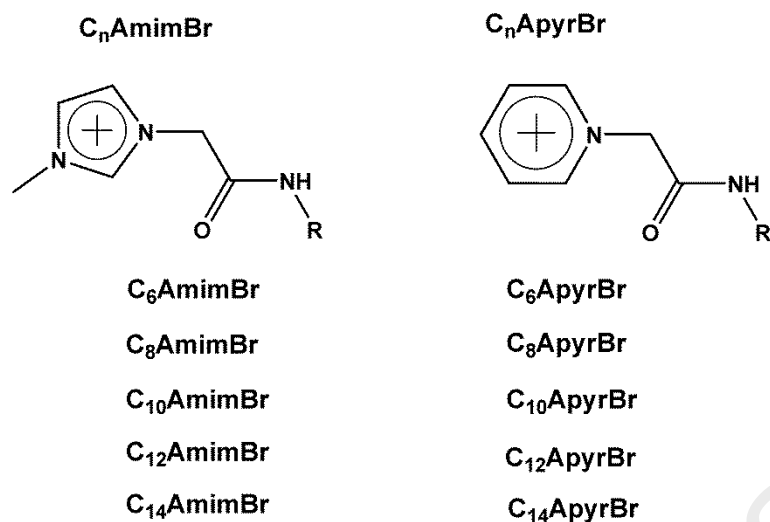
Figure 2.9: Amide-functionalized ILs by Garcia *et al.* (2014).

2.4 BIODEGRADABLE ILS

Every IL considers unique with distinct individual toxicity and biodegradation properties. Therefore, before applying IL in various applications, individual screening is preferable for each specific type as a part of assessment criteria (Coleman & Gathergood, 2010; Gilmore, 2011).

2.4.1 Toxicity and biodegradation of ILs

Hazard assessment of ILs has become an important area of research where many groups have reported their toxicity, ecotoxicity, bioaccumulation and biodegradation (Matsumoto, Mochiduki, Fukunishi, & Kondo, 2004; Matsumoto, Mochiduki, & Kondo, 2004; Pernak, Goc, *et al.*, 2004). In addition, the relative ease of obtaining toxicity data for a series of ILs compared to biodegradation data, and in particular bioaccumulation studies, is most likely the reason for the prioritisation of toxicity data. Thus, determination of the potential environmental impact of ILs has focused on toxicity data in previous studies where a comprehensive review of ILs toxicity presented by Zhao, Liao, and Zhang (2007). A highly desirable property in first generation design of 1-butyl-3-methylimidazolium [bmim] ILs was chemically stable beside their high solubility in water even those associating with lipophilic anions such as bis(tri-

fluoromethyl)sulphonyl amide [NTf$_2$], or hexafluorophosphate [PF$_6$] anions. These features have given ILs the versatility to be used in a wide variety of chemical reactions. However, ILs might also prove resistant to biological breakdown and could accumulate in the environment due to this stability. It is important to consider factors that influence the toxicity and biodegradation in the design stage of ILs. Biodegradation studies provide a preliminary toxicity assessment of ILs and their metabolites. Commonly, the IL was considered a resistant to biodegradation and has high potential to bioaccumulate when does not pass the biodegradation tests and vice versa. However, metabolite of the IL could be bio-accumulated, therefore, further studies of biodegradation, mineralisation and bioaccumulation are required to establish non-persist IL metabolites in the environment.

Generally, ILs contain substituted cation with long alkyl chain of carbons atoms, and also those with lipophilic anions, exhibited unfavourable toxicity (Stolte *et al.*, 2007; Swatloski *et al.*, 2004; Wells & Coombe, 2006). Wells and Coombe studied the toxicity and biodegradation for the library of imidazolium, pyridinium, ammonium, and phosphonium ILs, and also studied the counter anion effects by screening related salts or acids (*i.e.* NaPF$_6$, NaCH$_3$OSO$_3$, HN(SO$_2$CF$_3$)$_2$) (Table 2.2). The biochemical oxygen demand over 5 days (BOD$_5$) of the tested ILs was used to estimate the *readily biodegradable* ILs over all biodegradability results. Cations with short alkyl chains (C $\leq$ 4) did not undergo biodegradation over the period of the test. Only one short-chain test compound, sodium methylsulphate, showed detectable BOD during the test. However, it was apparent that imidazolium and pyridinium ILs with longer alkyl chains (C8, C12 and C18) exhibited an increase in toxicity to the tested species and most of the ILs displayed resistance to biological breakdown.

Table 2.2: Biodegradation data of ILs presented by Wells and Coombe (2006).

IL	Cation	% Inhibition of glucose/glutamate biodegradation at substance concentration			Measured biodegradation[a]
		100 mg L^{-1}	10 mg L^{-1}	1 mg L^{-1}	
[bmim][PF$_6$]	Imidazolium	9	8	28	0
[bmim][Cl]	Imidazolium	0	18	15	0
[dodecmim][Cl]	Imidazolium	97	59	3	Not tested[b]
[hexadecmim][Cl]	Imidazolium	100	100	16	Not tested[b]
[octadecmim][Cl]	Imidazolium	100	100	100	Not tested[b]
[1-Bupy][Cl]	Pyridinium	4	13	21	0
[1-Bu-1-EtPH$_2$][(EtO)$_2$PO$_2$]	Phosphonium	19	15	16	9
[1-Hex-1-tetradecylPH$_2$][Cl]	Phosphonium	100	100	78	Not tested[b]
[1-Oct-1-methylNH$_2$][NTf$_2$	Ammonium	23	37	26	0
[{C$_2$H$_4$O(C$_2$H$_4$O)$_4$Me}$_2$C$_{14}$H$_{29}$NH$_2$] [MeSO$_4$]	Ammonium	100	100	47	Not tested[b]
NaPF$_6$	-	-	-	-	Inorganic
NaCH$_3$OSO$_3$	-	-	-	-	Not tested[c]
HN(SO$_2$CF$_3$)$_2$					0[d]

[a] % oxygen uptake (biodegradation) after 28 days) BOD/measured COD, [b] Inhibitory at test concentration, [c] BOD$_5$ result shows material is readily biodegradable, [d] Note low carbon content of substrate.

Moreover, the acute toxicity and biodegradability of several imidazolium-based ILs (Figure 2.10) in the aqueous phase have studied by Romero, Santos, Tojo, and Rodriguez (2008). The Microtox[R] Protocol was used to investigate the EC50 and acute toxicity of these compounds; (EC50 is defined as the effective nominal concentration of the toxic chemical (in mg/L) that reduces the intensity of light emission by 50%). The group reported a correlation between alkyl chain length and toxicity, which was in agreement with Wells' study (Wells & Coombe, 2006). It was found that the shorter R alkyl chain displayed the lowest toxic effect. Biodegradability was analysed using

(BOD$_5$) with aqueous samples containing known initial concentrations of the compounds and/or D-glucose (as a carbon source).
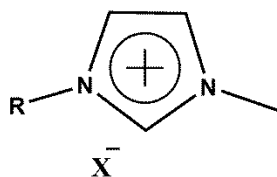
1 R = (CH$_2$)$_3$CH$_3$, X = Cl
2 R = CH$_3$, X = CH$_3$OSO$_3$
3 R = CH$_2$CH$_3$, X = CH$_3$CH$_2$OSO$_3$
4 R = (CH$_2$)$_5$CH$_3$, X = Cl
5 R = (CH$_2$)$_7$CH$_3$, X = Cl
6 R = (CH$_2$)$_5$CH$_3$, X = PF$_6$
7 R = (CH$_2$)$_7$CH$_3$, X = PF$_6$

Figure 2.10: Imidazolium-based ILs prepared and screened by Romero *et al.* (2008).

Further, toxicity and biodegradation for a library of 66 ILs containing oxygenated side chains and amides were reported by Morrissey *et al.* (2009). Antimicrobial activity of the ILs screened against four Gram negative strains of bacteria: *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella sp.*, *Salmonella sp.* and three Gram positive bacteria: *Staphylococcus aureus*, *Enterococcus sp.*, *Bacillus subtilis*. A significant reduction in toxicity for the ILs containing ether or poly ether side chains (MIC values 420 mg mL^{-1}, corresponding to low toxicity at concentrations of 427 mM to 475 mM) compared with those bearing long chain alkylimidazolium salts was observed. Fifteen ILs (Figures 2.11 and 2.12) were studied for biodegradation and six of these were classified as *readily biodegradable* by using the CO$_2$ headspace test.
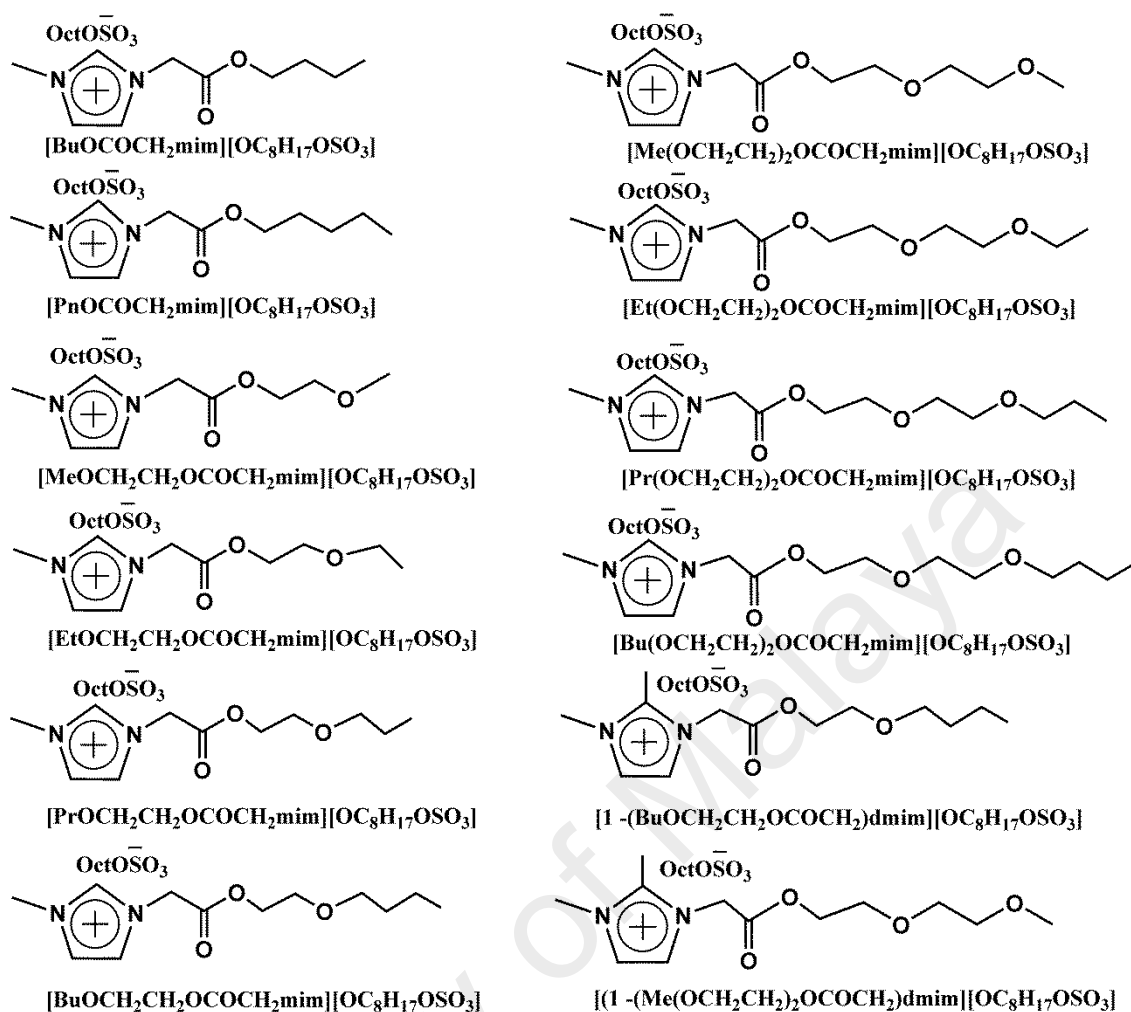
Figure 2.11: Imidazolium ILs contain oxygen-functionalised esters prepared and screened for biodegradation by Morrissey *et al.* (2009).
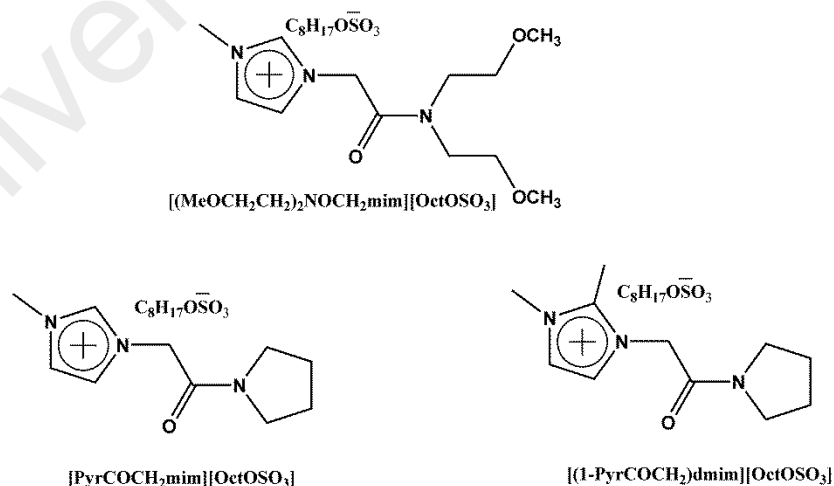
Figure 2.12: Amide functionalised ILs investigated using the CO_2 headspace test.

More detail studies related biodegradation of imidazolium ILs are mentioned in section 2.3.6.

2.4.2 Chemical structure of the biodegradable compounds

The pioneering work (Boethling, 1994; Boethling, 1996; Howard, Boethling, Stiteler, Meylan, & Beauman, 1991) in the design of biodegradable chemicals has greatly assisted researchers in the field of ILs by laying down guidelines for the synthesis of environmentally benign solvents. Boethling *et al.* highlighted number of factors that can improve the mineralisation of organic compounds by mixed microbial communities. An increase in aerobic biodegradation is usually observed for those compounds that contain the following structural motifs:

i. Benzene 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).

However, increased resistance to aerobic biodegradation is generally observed for those compounds which contain the following structural motifs:

i. halogens; with chlorine and fluorine being particularly persistent

ii. chain branching; particularly where tertiary nitrogens or quaternary carbons are part of the structure, or where multiple branches are present in the same molecule

iii. nitro, nitroso, azo and arylamino groups

iv. polycyclic frameworks of the kind encountered in fused aromatic hydrocarbons (*e.g.* benzo[*a*]pyrene)

v. heterocycles (*e.g.* pyridine rings)

vi. aliphatic ethers

It must be strongly emphasised that these factors are only guidelines and that the presence of a single desirable or undesirable motif within a molecule does not guarantee

either biodegradability or persistence in the environment. Generally, the enzymes of microbial communities play a major role in the biodegradation and the process improved with the substrate contains ester linkages.

The oxidase enzymes involved can even act upon species that would normally be considered inert, such as unsubstituted alkyl chains and aromatic rings. In the environment this step is carried out by bacteria and is frequently the rate-limiting step in the degradation of organic molecules (Boethling, Sommer, & DiFiore, 2007). In particular, unsubstituted alkyl chains with greater than four carbons, and also benzene rings provide possible sites for being attacked by oxygenases and are especially beneficial when hydroxylation is required to increase solubility and aid excretion of a potential toxin.

2.4.3. Biodegradation assays

Biodegradation assays are generally carried out according to OECD Guidelines for Testing of Chemicals: a series of guidelines laid down by the Organisation for Economic Co-operation and Development with the aim of reproducibly assessing the effects of chemicals on workers and the environment. Commonly used terms and abbreviations in accordance with OECD Guidelines (OECD; OECD) include:

Biodegradation: conversion or breakdown of a chemical structure catalysed by enzymes in vitro or in vivo, resulting in loss of specific properties, especially biological activity.

Readily biodegradable: an arbitrary classification of chemicals that have passed certain specified screening tests for ultimate biodegradability; these tests are so stringent that it is assumed that such compounds will rapidly and completely biodegrade in aquatic environments under aerobic conditions.

Ultimate biodegradation: the level of degradation achieved when the test compound is totally utilised by micro- organisms resulting in the production of carbon dioxide, water, mineral salts and new microbial cellular constituents (biomass).

Primary biodegradation: an alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance.

Mineralisation: the complete degradation of an organic compound to small molecules, such as carbon dioxide and water under aerobic conditions and carbon dioxide, water and methane under anaerobic conditions.

Inoculum: the source of microorganisms used to carry out biodegradation of the test substance; typically this may be derived from a variety of sources: activated sludge, sewage effluents (unchlorinated), surface waters and soils, or from a mixture of these.

Bioaccumulation: gradual build up over time of a chemical in a living organism.

DOC: dissolved organic carbon (DOC per L) is the organic carbon present in solution or that which passes through a 0.45 μm filter or remains in the supernatant after centrifuging at approximately 4000 g (around 40 000 ms^{-2}) for 15 minutes.

TOC: total organic carbon is the sum of the organic carbon in solution and in suspension.

BOD: biochemical oxygen demand is the amount (mg) of oxygen consumed by microorganisms when metabolising a test substance.

COD: chemical oxygen demand is the amount (mg) of oxygen consumed during the oxidation of a test compound with hot acidic dichromate; it provides a measure of the amount of oxidisable matter present.

10-day window: the ten days immediately following the attainment of 10% biodegradation.

The biodegradability of ILs has been evaluated using a number of standard methods. The most commonly used tests are the modified Sturm and closed bottle tests (OECD 301 B and D, respectively), the DOC Die-Away Test (OECD 301 A) and also the CO_2 headspace test (ISO 14593), which is the reference method for laboratory testing of ultimate biodegradability.

Each method has a relative principle of the test, whereby the degradation is monitored by the determination of parameters such as dissolved organic carbon (DOC), carbon dioxide production and oxygen uptake. Measurements of these parameters are taken at sufficiently frequent intervals, in order to identify the beginning and end of the biodegradation. Typically the tests are performed over a 28 day period; however, tests may be ended before the 28-day time frame if the biodegradation curve has reached a plateau for the last three measurements. Furthermore, the tests can be extended beyond the 28 days when the biodegradation curve has shown that biodegradation has started but the plateau has not been reached by the last day (day 28). In the latter case, the chemical would not be deemed *readily biodegradable*. The method used to assess the biodegradation of organic chemicals depends on several fundamental physical properties of the compound in question, *i.e.* whether the test substance is soluble in water (to at least 100 mg L^{-1}), volatile or adsorbing in nature. Table 2.3 demonstrates the applicability of the biodegradation standard methods based on the properties of the test compound. However, each test method varies depending on the parameters investigated during the test (DOC, CO_2 evolution or O_2 consumption) and also on the general procedure and preparations followed.

Table 2.3: Suitability of OECD biodegradation methods by Coleman and Gathergood (2010).

Biodegradation standard method	Analytical factor estimated	Suitability for compounds which are:		
		Poorly soluble	Volatile	Adsorbing
DOC Die-Away (301 A)	Dissolved organic carbon (DOC)	−	−	±
CO_2 evolution (301 B)	Respirometry: CO_2 evolution	+	−	+
Closed bottle (301 D)	Respirometry: dissolved oxygen	±	+	+
Modified OECD screening (301 E)	Dissolved organic carbon (DOC)	−	−	±
CO_2 headspace test (ISO 14593)	CO_2 evolution	+	+	+
OECD 309	^{14}C labelling	±	+	+
Manometric respirometry (301 F)	Oxygen consumption	+	±	+

+: Suitable method to screen compound;
−: unsuitable method to screen compound.

2.4.4. Biodegradation curve

Biodegradation curve can be obtained by plotting the percentage of biodegradation against incubation time as shown in Figure 2.13. The biodegradation phase, lag phase, 10-day window and plateau phase (define as the phase in which the maximal degradation has been reached and the biodegradation curve has levelled out), are indicated by the graph of the test and reference substances. Generally, the mean values of the percentage biodegradation are used to plot the biodegradation curve where the plateau phase is determined or the highest value is assessed.
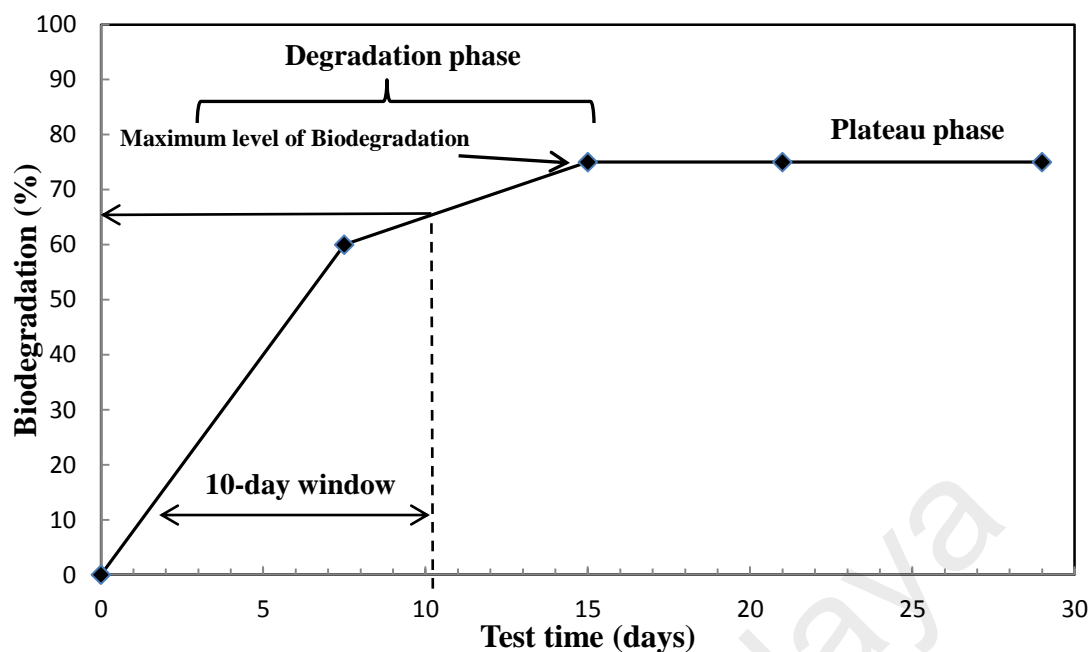
Figure 2.13: Example of biodegradation curve using the CO_2 headspace test (OECD).

2.4.5 Biodegradation studies of ILs

Despite ILs appearing increasingly in the research literature for over a last two decades (Welton, 1999), biodegradation data for this class of compounds have only appeared in recent years. Primary biodegradation studies and metabolite profiling of imidazolium (Gathergood, Garcia, & Scammells, 2004; Gathergood, Scammells, & Garcia, 2006), pyridinium (Harjani, Singer, Garcia, & Scammells, 2009), ammonium (Klein *et al.*, 2013; Yu *et al.*, 2008), and phosphonium (Atefi, Garcia, Singer, & Scammells, 2009) ILs were discussed in the literature. Further studies for pyrrolidinium, morpholinium, piperidinium (Neumann, Steudte, Cho, Thoming, & Stolte, 2014), and bio-renewable ILs (Ferlin *et al.*, 2013; Gore & Gathergood, 2013) have been performed more recent. These studies included methods of identifying metabolites arising from ILs biodegradation as well as the possible pathways occurring during the biological breakdown. However, the biodegradation data that work to determine possible pathways for the biodegradation of ILs is still at an early stage. Varieties of analytical techniques have been used to identify possible metabolites of ILs.

Biodegradation studies of ILs are especially important due to a possible metabolite may display toxicity and persist in the environment, even if the parent ionic liquid is non-toxic and appears to be biodegradable. ^{1}H-NMR analysis has been used by Docherty, Dixon, and Kulpa Jr (2007), to investigate the biodegradation of a number of commonly used ILs. Six ILs consisting of imidazolium and pyridinium bromide salts with linear-butyl, -hexyl and -octyl alkyl side chains were subjected to biodegradation by an activated sludge (Figure 2.14). A modified OECD (Organisation for Economic Co-operation and Development) guideline for the testing of chemicals standard dissolved organic carbon (DOC) Die-Away test was used to perform the biodegradation analysis of the tested ILs. Results obtained by Docherty *et al.* suggested that pyridinium ILs are generally more biodegradable than comparable imidazolium ILs. Further, longer alkyl chain length compounds are more readily degradable than compounds with shorter alkyl chains. Of the six ILs screened, only one example [3-Me-1-Octpy][Br] could be classified as readily biodegradable according to the DOC Die-Away test guidelines; with biodegradation 96% after 25 days.
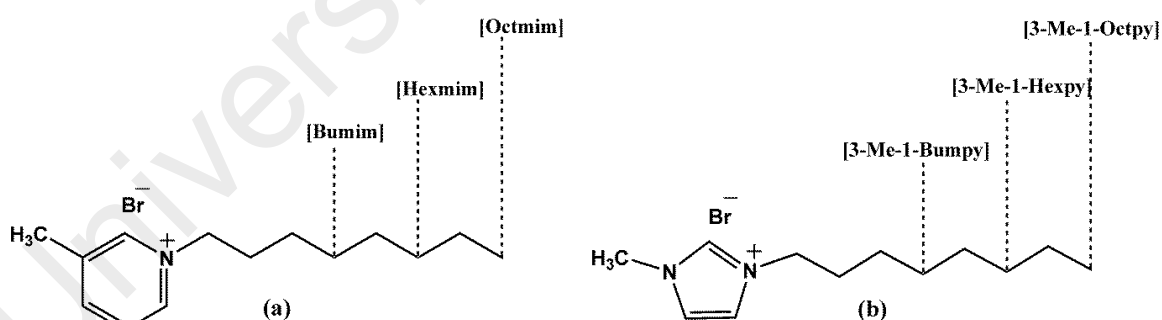
Figure 2.14: Chemical structures of the six (a) imidazolium and (b) pyridinium ILs presented by Docherty *et al.* (2007).

Based on OECD guideline 301 D, primary biodegradation of different *N*-imida-zoles, imidazolium, pyridinium and 4-(dimethyl-amino)-pyridinium ILs with various alkyl side chains (C2–C8) presented by Stolte *et al.* (2008). The samples were analysed using HPLC-MS to determine possible metabolites formed upon mineralisation by the

activated sludge community with the aim of deducing pathways of IL degradation. Adsorption of the test compounds to the sludge was investigated using an abiotic control. From the 27 substances tested and also some simple mono *N*-substituted imidazoles, no sorption to the sludge was indicated (Figure 2.15). By HPLC-MS analysis for the metabolites of biodegradation test and based on the mass ions observed, Stolte and co-workers proposed two possible metabolic pathways for the biodegradation.
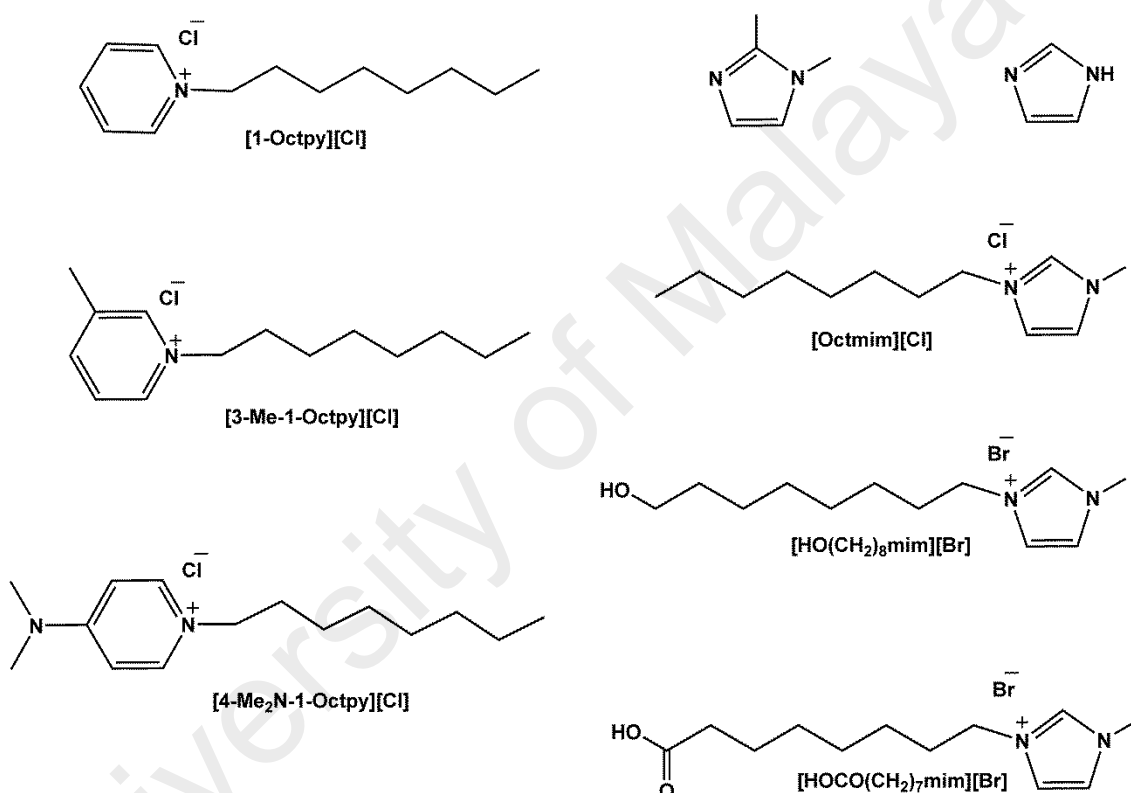
Figure 2.15: ILs and *N*-imidazole controls with 100% primary biodegradation within 31 days by Stolte *et al.* (2008).

Harjani *et al*. presented studies including design, synthesis and biodegradability screened for pyridinium ILs (Harjani, Singer, Garcia, & Scammells, 2008; Harjani, Singer, *et al.*, 2009). These ILs were prepared from pyridine or nicotinic acid as cheap and readily available starting materials. By using the CO_2 headspace test (ISO 14593), ILs that showed biodegradation level higher than 60% are considered as ''*readily biodegradable*''. The biodegradability does not seem to significantly depend on the

anion, although some effects are apparent. The 1-alkylpyridinium ILs with linear chain; C4, C10 and C16, displayed relatively low levels of biodegradability, while ILs with a pyridinium cation bearing an ester containing substituent at positions 1 or 3 showed excellent biodegradability. The introduction of a methyl group to the 3-position of the pyridinium core did not display biodegradation of ILs increasing. Figure 2.16 illustrates the chemical structures of pyridinium low and *readily biodegradable* ILs prepared by Harjani *et al*.

X = Br   [1-Bupy][Br]
X = $C_8H_{17}OSO_3$ [1-Bupy][$C_8H_{17}OSO_3$]
X = NTf_2 [1-Bupy][NTf_2]
X = PF_6 [1-Bupy][PF_6]

X = Br   [3-Me-1-Bupy][Br]
X = $C_8H_{17}OSO_3$ [3-Me-1-Bupy][$C_8H_{17}OSO_3$]
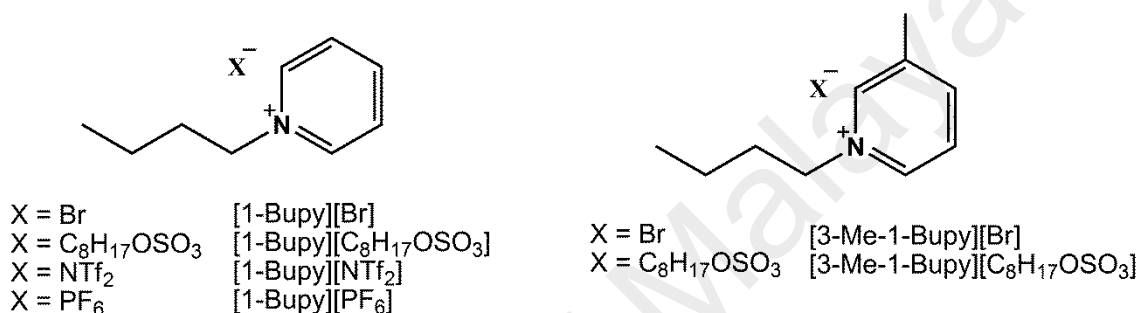
(a) 1-Butylpyridinium ILs showed low biodegradability

[1-Decpy][Br]

[1-Hexadecpy][Br]

(b) 1-Alkyl pyridinium bromides ILs showed low biodegradability

X = Br   [1-EtOCOCH$_2$py][Br]
X = $C_8H_{17}OSO_3$ [1-EtOCOCH$_2$py][$C_8H_{17}OSO_3$]
X = NTf_2 [1-EtOCOCH$_2$py][NTf_2]
X = PF_6 [1-EtOCOCH$_2$py][PF_6]
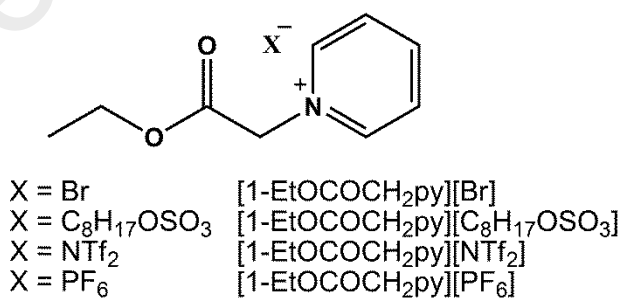
(c) Readily biodegradable pyridinium ILs with 1-alkyl ester side chain

Figure 2.16: Pyridinium ILs prepared and investigated using the CO_2 headspace test by Harjani, Singer, *et al.* (2009).

The investigation of metabolites formation as a result of biodegradation of 1-butyl-3-methylpyridinium bromide was carried out for the first time by Pham, Cho, Jeon, *et al.*

(2008). Their biodegradation was studied using an activated sludge assay (OECD 301 E). According to HPLC-MS analysis degradation results, two possible pathways for the biodegradation of *N*-butyl-3-methylpyridinium bromide were suggested. The first pathway (I) hypothesised the IL may be undergoes an enzymatic oxidation to be converted into an *N*-hydroxybutyl-4-(3-methylpyridinium) cation. While the putative second pathways (II) suggested hydroxylation process of C2 of the alkyl chain to produce an *N*-(2-hydroxybutyl)-3-methylpyridinium cation. At the end of either pathway (I) or (II) a final fragmentation of the *N*-(2-hydroxyethyl)-3-methylpyridinium fragment under HPLC-MS conditions may occur in which loss of ethane giving the 3-methylpyridinium cation. However, the authors were unable to confirm whether this ion was merely an artefact from 3-methylpyridine contaminating the IL stock solution.

Yu *et al.* (2008) reported the preparation of ten biodegradable choline-based ILs with naphthenic acid derivatives as counter anions. These naphthenic acid ILs (NAILs) were obtained by one-pot neutralisation of the corresponding acids with choline hydroxide. Naphthenic acid surrogates were chosen due to their biodegradability to carbon dioxide and methane. As compared to other commonly used metathesis reactions to produce ILs, the minimal waste produced as well to negligible halogen contamination (*i.e.* high purity) were the major advantages of this one-pot synthesis. By using the 'Closed Bottle Test' eight of the ten prepared NAILs are shown as *ready biodegradable* ILs (biodegradation ≥60%). Figure 2.17 (a) demonstrates the chemical structures of NAILs, which passed the 'Closed Bottle Test', while (b) depicts the two ILs; choline 2-naphthoxyacetate [Ch][NOA] and choline anthracene-9-carboxylate [Ch][AC], that failed in the biodegradability test. The decrease in biodegradability is in accordance with Boethling's factors that polycyclic moieties (especially polycyclic aromatic hydrocarbons) can cause an increasing in resistance to biological breakdown (Boethling *et al.*, 2007).

Besides testing the novel NAILs, Yu and co-workers also screened a number of commercially available ILs and organic solvents. They compared the biodegradability of the NAILs with highly biodegradable organic solvent; ethanol, where the commonly used ILs presented the lower levels of biodegradation. Generally, choline-based quaternary ammonium salts are highly promising biodegradable ILs showing stimulating effect on activated sludge in wastewater treatment plants. The biodegradation data related to quaternary ammonium-based surfactants are widely reported in literature (Brycki, Waligórska, & Szulc, 2014; Grabińska-Sota, 2011; Klein *et al.*, 2013). Regarding surfactant industry as an example, the design features that are incorporated into ILs are: (*i*) avoiding branched hydrocarbon chains, (*ii*) including hydrolysable groups (*e.g.* esters and amides), and (*iii*) the presence of ether groups with linear alkyl chains ≥ C4. As a general rule all these features have contributed in improving biodegradation of surfactant ILs (Coleman & Gathergood, 2010).
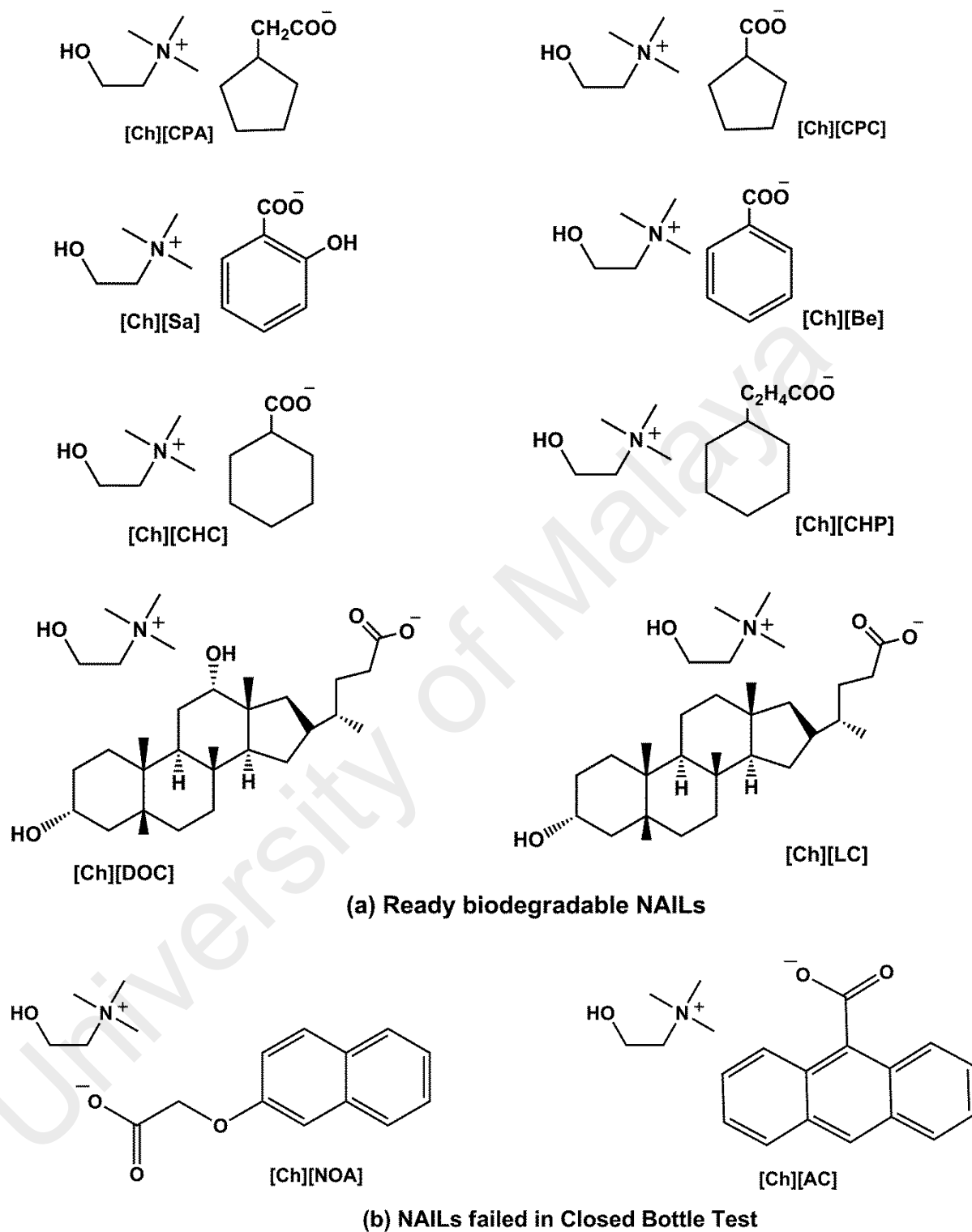
Figure 2.17: NAILs presented by Yu *et al.* (2008); (a) *Ready biodegradable*, (b) ILs failed in Closed Bottle Test.

2.4.6 Biodegradation of Imidazolium based ILs

Gathergood and Scammells (2002) were the first to undertake biodegradation studies of ILs in which they introduced functional groups that would be susceptible to enzymatic hydrolysis (ester/amides) into the IL cation side chain. Biodegradation of the resulting 3-methyl-1-(alkyloxycarbonylmethyl)imidazolium ILs was then compared with that of the commonly used dialkylimidazolium salts, [bmim][BF$_4$] and [bmim][PF$_6$], using the modified Sturm and 'Closed Bottle Tests' (OECD 301 B and D, respectively). Compounds which reached a biodegradation level higher than 60% are referred to as ''*readily biodegradable*''.

Following this study, a 'Closed Bottle Test' (OECD 301D) was used to screen a large panel of ILs with ester and amide side chains (Gathergood *et al.*, 2004). In this preliminary evaluation study of the biodegradation, the IL (2 mg L^{-1}) was added to an aerobic mineral medium inoculated with waste-water sludge and the depletion of dissolved oxygen was measured over 28 days. A control inoculum was run in parallel to determine oxygen blanks and sodium *n*-dodecyl sulphate (SDS) used as the reference standard. Incorporation of an ester into the IL side chain significantly improved the biodegradation, whereas the amide derivatives displayed poor biodegradability. The presence of an ester bond in the side chain provides a site for possible enzymatic cleavage to give the parent imidazolium fragment and the corresponding primary alcohol that may be readily metabolised via fatty acid β-oxidation. Esters with an alkyl side chain of ≥ 4 carbons proved to be the most biodegradable of the series. These initial results encouraged Gathergood's research group to elucidate the effect of the anion on the biodegradation of ILs (Garcia, Gathergood, & Scammells, 2005). A series of ester-functionalised ILs with a variety of different anions (Figure 2.18) were compared with [bmim][Br] examples. Again, the 'Closed Bottle Test' was used to compare the biodegradability of the two classes of IL. From the data it could be seen that the 3-

methyl-1-(propoxycarbonyl)-imidazolium series showed higher levels of biodegradation, compared with the 1-butyl-3-methylimidazolium derivatives. In particular, when the octylsulphate ($C_8H_{17}OSO_3$) anion was incorporated into the IL, an increase in biodegradation was observed (49% degradation after 28 days). The overall increasing in the measured biodegradation is attributed to the high propensity for the octylsulphate anion to degrade. This provides higher biodegradation values comparing to the screened ILs that incorporated into other anions. The imidazolium core did not undergo biodegradation in this test, as exemplified by the negligible breakdown on [bmim][Br] under the test conditions.

X^-

X = Br
X = BF_4
X = PF_6
X = NTf_2
X = $N(CN)_2$
X = $C_8H_{17}OSO_3$

X^-

X = Br
X = BF_4
X = PF_6
X = NTf_2
X = $N(CN)_2$
X = $C_8H_{17}OSO_3$
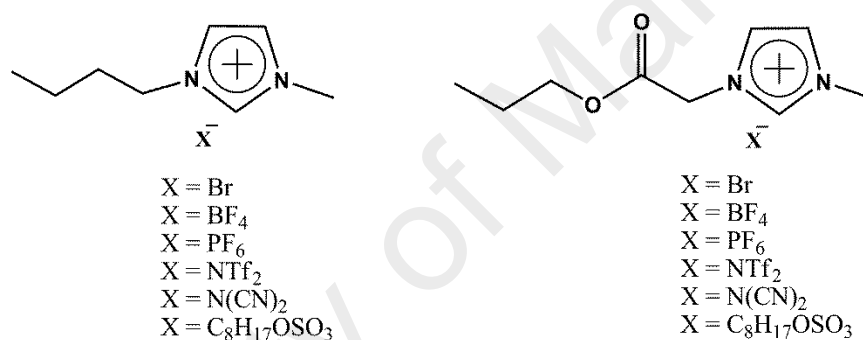
Figure 2.18: ILs screened using 'Closed Bottle Test' by Garcia *et al.* (2005).

Finally this research has identified the first ILs which can be classified as '*readily biodegradable*' (above 60% biodegradation over 28 days) under aerobic conditions. 'Closed Bottle' and 'CO₂ Headspace' tests (OECD 301D and ISO 14593) were applied to evaluate the biodegradability of the target ILs (Gathergood *et al.*, 2006). The biodegradation results recorded using the CO_2 headspace test were higher than those obtained by the 'Closed Bottle Test'. These differences may be attributed to the higher bacterial cell density in the inoculum used in the CO_2 headspace test (Coleman & Gathergood, 2010).

2.5 SURFACTANTS (SURFACE ACTIVE AGENT)

A surfactant (abbreviated form of surface-active agent) is an amphiphilic organic molecule. Surfactants contain both hydrophobic (tail) and hydrophilic (head) groups, and the presence of these two antipodes determines the physicochemical properties of surfactants in a solution (Figure 2.19) for both aqueous and non-aqueous media.
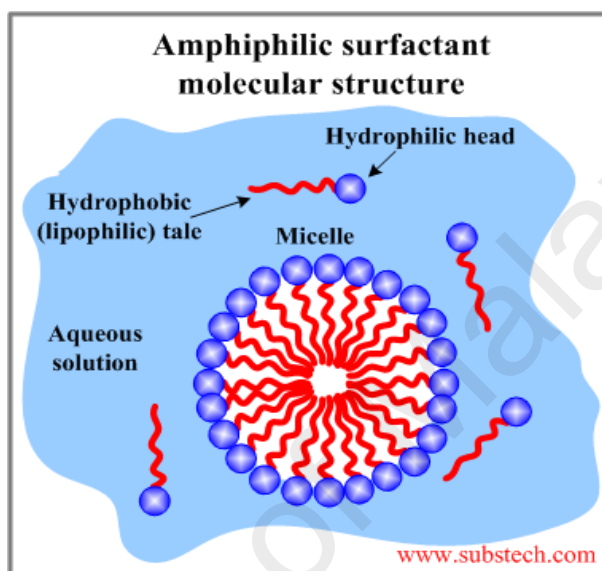
Figure 2.19: Surfactant molecule showing hydrophilic and hydrophobic components by Kopeliovich (2013).

The amphiphilic nature of non-ionic surfactants makes the hydrophilic heads of the surfactant molecules dissolve in the water phase, while the hydrophobic tails tend to aggregate at the interfaces. Through this way they modify the surface tension of an aqueous solution, reducing the surface or interfacial tension and stabilizing foam. In aqueous systems surfactant molecules tend to form a layer at the air–water interface until saturation is reached. Above the molecular solubility, further addition of surfactants to the bulk liquid leads to the formation of aggregates (clusters), which are larger than the molecular dissolved surfactant. The surfactant self-organizes into micelles, which can effectively facilitate the micro-solubilisation or emulsification of an otherwise insoluble organic phase (Van Oss, 2008). The critical micelle concentration is the minimum surfactant concentration at which the surface or interfacial tension initially

reaches the lowest value, indicating that the surfactant molecules self-aggregate in solution.

Surfactants are increasingly distributed and developed for utilization in various industries such as detergents, emulsifiers, wetting agents and defoamers like in: fabric softeners, formulations and paints. They have emerged as product group with highest market volume in the chemical sector. In view of their tremendous consumption, the synthesis of surfactants should focus on producing environmental compatible materials. The use of renewable resource materials provides good prospects for this.

2.6 CLASSIFICATION OF SURFACTANTS

Surfactant can be classified into two categories either chemical or biological surfactants based on their source. Biological surfactants are mostly produced by microorganisms during the process of microbial activities. They exhibit unique properties, such as mild production condition, low toxicity, high biodegradability and environmental compatibility (Desai & Banat, 1997; Kitamoto, Isoda, & Nakahara, 2002; Van Hamme, Singh, & Ward, 2003). On the other hand, chemical surfactants are more economic. There are numerous classifications for chemical surfactants. An important classification emphasizes on the charge of the hydrophilic head group; surfactants are grouped into ionic (both cationic and anionic), non-ionic and zwitterionic surfactants (Mishra *et al.*, 2009) as shown in Figure 2.20.
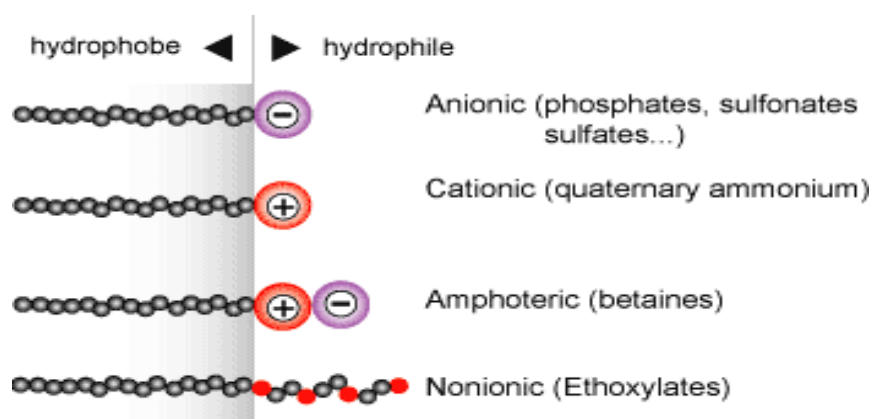
Figure 2.20: Schematic structure of surfactant types. ("How to disperse and stabilize pigments ", 2015)

The hydrophobic "tail" group of surfactant can range from simple hydrocarbon chains, which may be straight or branched, and either saturated or unsaturated, over complex aromatics and fluoro-carbon chains to siloxanes.

2.6.1 Cationic surfactants

Cationic surfactants are commonly amines and ammonium salts. The vast majority of cationic surfactants are imidazolines, benzimidazol, ammonium salt and quaternary ammonium compounds (Bajpai & Tyagi, 2006; Kang, Lee, Hwang, & Lim, 2011). Usually amine-based cationic surfactants are applied in protonated state, *i.e.* at acidic pH. Examples are shown in Figure 2.21. Cationic surfactants are found to be used in industrial sectors such as antistatic additives (particularly for textiles), as well as bitumen emulsifiers, personal care formulations and as softeners. However, a limitation in their usage for bulk products (like detergents) are exposed due to their high hydrolytic stability and th toxicity exceeds other surfactant classes (Alkhatib, 2006; Cowan-Ellsberry *et al.*, 2014; Holmberg, Jönsson, Kronberg, & Lindman, 2003).
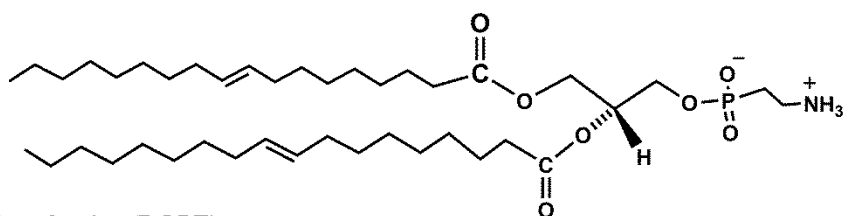
Di-oleoylphosphatidylethanolamine (DOPE)
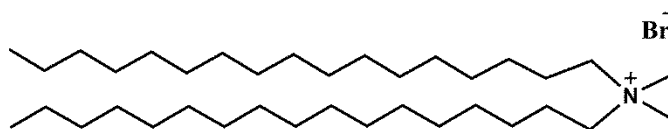
Di-dodecyldimethyl ammonium bromide (DDAB)
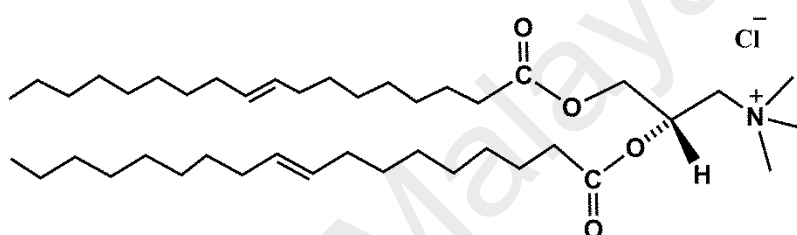
1,2-dioleoyl-3- trimethylammonium propane (DOTAP)

Figure 2.21: Structure of the most common cationic surfactants (Alkhatib, 2006).

2.6.2 Anionic surfactants

The most common head groups of these surfactants are sulphate, carboxylate and sulphonate in combination with sodium or potassium cations. The behaviour of anionic surfactants is easily affected by the pH of the medium. The acid sensitivity decreases in the following order: carboxylate > phosphate > sulphate ~ sulphonate. Figure 2.22 shows the most common types of anionic surfactants.
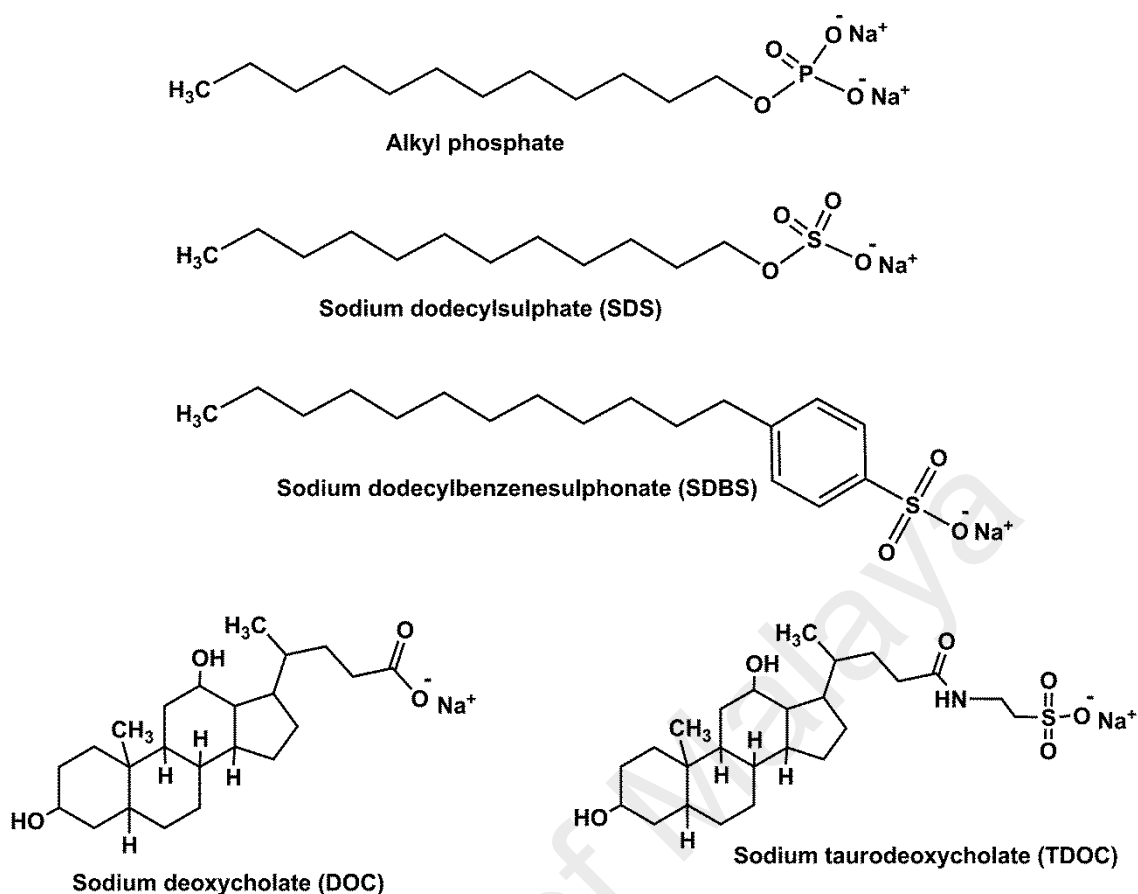
Figure 2.22: Structure of the most common anionic surfactants.

2.6.3 Zwitterionic surfactants

Zwitterionic or amphoteric surfactants consist of two oppositely charges in the head group. The positive charge is almost invariably in an ammonium ion, while the negative charge mostly refers to carboxylates in synthetic surfactants and phosphates are more common for biological analogs. Due to their high prices obstacles, Zwitterionic surfactants are seldom used. The structures of common types of this surfactant are depicted in Figure 2.23. They are generally stable in a wide range of pH (acidic and basic media) and exhibit low toxicity; therefore they are used partially in personal care products and antibacterial agent, (Alargova *et al.*, 1998; FernLey, 1978; Gawish, Hazzaa, Zourab, & El-Din Gebril, 1981).
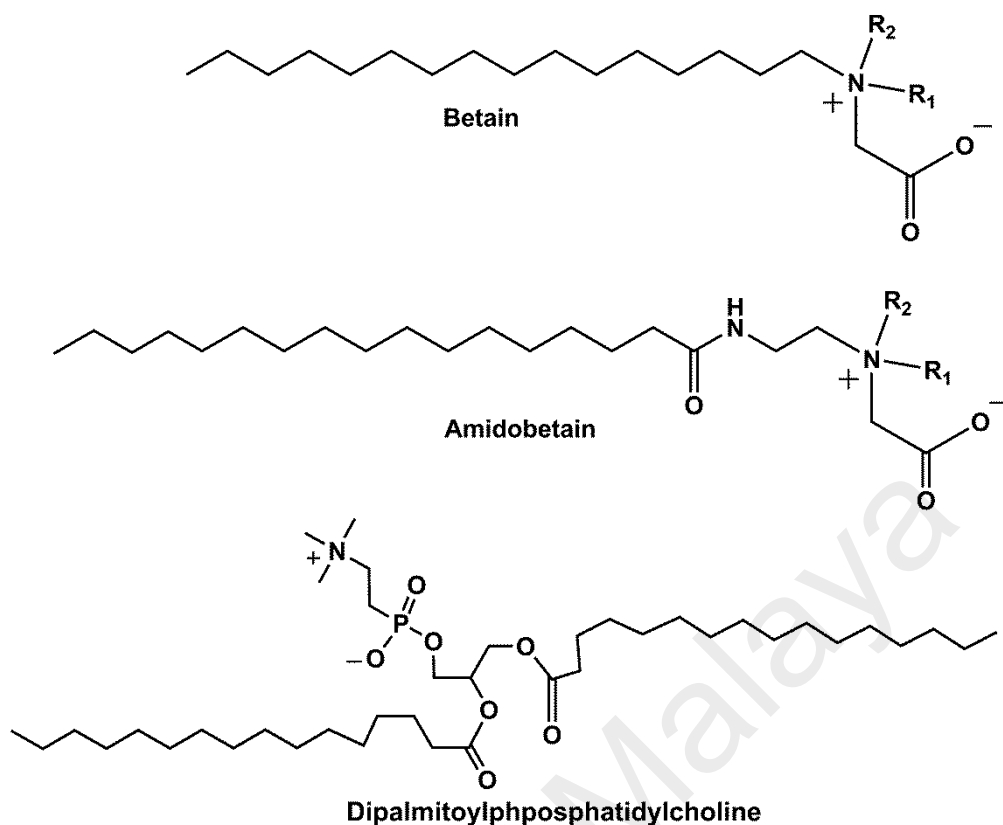
Figure 2.23: Structure of some zwitterionic surfactants, R_1 and R_2 different lengths of alkyl group (Alkhatib, 2006; Holmberg *et al.*, 2003).

2.6.4 Non-ionic surfactant

Non-ionic surfactants have a non-charged polar head group, which either comprises of a polyether or polyalcohol (for example sorbitan and sucrose esters, alkyl glycoside and, polyethylene glycol ethers). Various structures of non-ionic surfactants are depicted in Figure 2.24. Comparing to other surfactant types, non-ionic surfactant have some advantages, according to their minor sensitivity to electrolytes and much lower binding to biomolecules (like proteins) (Alkhatib, 2006) (Holmberg *et al.*, 2003). Lower toxicity, compatibility with other surfactant types and high salinity media are other advantages. Because of these favours, they are the most commonly used surfactants in the wide field of scopes. Non-ionic surfactants can be divided into esters, ethers and amides based on the nature of the linkage between the hydrophilic and hydrophobic domain.
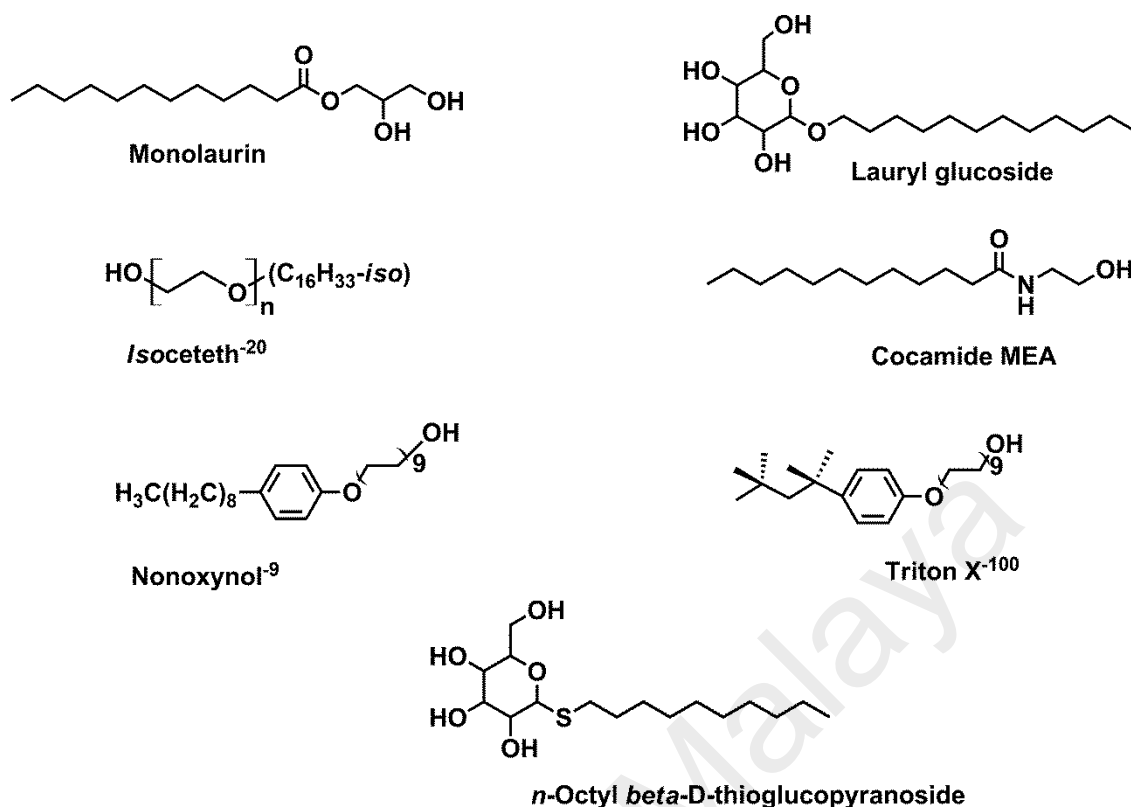
Figure 2.24: Structure of the most common non-ionic surfactants.

2.7 PHASE BEHAVIOUR

Surfactant molecules consist of hydrophilic and lipophilic domains. The presence of these incompatible regions makes them amphiphilic. When surfactants are dispersed in water, they adsorb at the air-water interface. The hydrophilic domain interacts with water, while the lipophilic (hydrophobic) domain points towards the air, *i.e.* away from the water. When the air-water interface is saturated with surfactants additional surfactant forms aggregate, which are termed 'micelles'. This aggregate formation is illustrated in Figure 2.25.
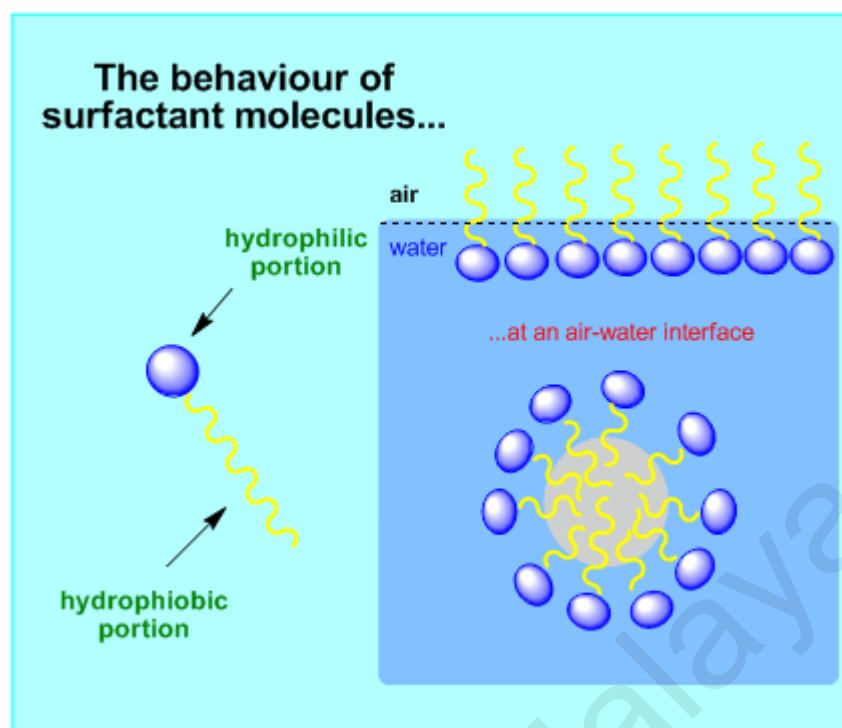
Figure 2.25: Behaviour of surfactant molecules in water ("Surfactant Molecules," 2015).

The self-assembly of surfactants in micelles occurs at short time scales (Jensen *et al.*, 2013). The hydrophobic domain of the surfactant forms the core of the micelles, while the hydrophilic domain ensures the interaction of the aggregate with the aqueous environment, as depicted in Figure 2.26. The aggregation is driven by hydrophobic effect, which can be understood thermodynamically as maintenance of the hydrogen-bonding network in water by avoiding disturbances due to the interaction of the hydrophobic domain with water molecules. At higher concentration, the self-assembly of surfactants turns into a macroscopic ordered structure; a liquid crystalline phase. More details are discussed in section 2.5.
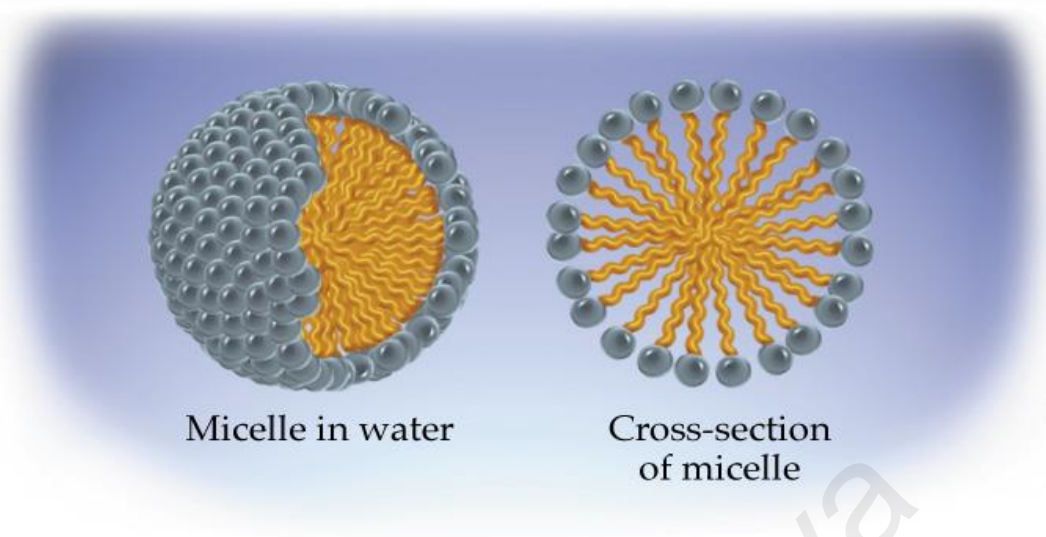
Figure 2.26: Self-assembly of surfactant molecules in micelles from ("ON MICELLES, VESICLES AND ARTIFICIAL CELLS-The Magic Of Directed Self Assembly," 2012).

2.8   SURFACTANT   MOLECULAR   STRUCTURE   AND   RELATED ASSEMBLIES

2.8.1 The packing parameter

The simplest aggregate of surfactant molecules in water or oil is called a micelle, and surfactant solutions (water or oil) are commonly referred to as micellar solutions (Goyal & Aswal, 2001). Micelles are important in a wide range of fields, such as biochemistry, pharmacy, chemistry, and medicine. They are applied for augmenting and controlled solubilisation, enhancing oil recovery and regulating chemical reaction rates. Their presence determines various properties of the surfactant solution, such as viscosity, capacity to solubilize water-insoluble materials and cloud point.

Micelles may appear in different shapes (Figure 2.27): (1) relatively small, spherical, and prevalent; (2) ellipsoidal, elongated cylindrical (rod-like) micelles with hemispherical ends; (3) large, flat lamellar micelles (dislike extends oblate spheroids) (Goyal & Aswal, 2001; Moulik, 1996; Nagarajan, 2002; Rosen, 2004). The shapes may change into each other, for example spherical micelles of sodium dodecyl sulphate (SDS) changing into a cylindrical configuration in a saline environment (Hayashi & Ikeda, 1980; Moulik, 1996). Parameters such as temperature, overall surfactant

concentration, pH, ionic strength, surfactant composition and liquid phase additives affect both, the aggregation number and the shape of a micelle (Rosen, 2004). The calculation principles for the micellar packing shape are relatively straight forward. Aggregated structures have lower energy than isolated molecules in the solution (Fisher, 2000). However, the actual shape of the aggregate can be determined on the basis of the geometry constraints for various micelle shapes and the space occupied by the hydrophilic and hydrophobic groups of the related surfactant molecules. The packing parameter, $V_H/L_c a_o$, is facilitated to determine the shape of the micelle (Rosen, 2004; Rosen & Kunjappu, 2012); where V_H = volume of the hydrophobic groups in the micelle core, a_o = optimal cross-section area occupied by the hydrophilic groups and L_c = critical chain length (hydrophobic group) in the core (Figure 2.27).

Therefore, the packing parameter can be defined as a measure of the curvature of the molecular aggregate, that is, the ratio of the tail volume to the optimal head group area. A small packing parameter indicates a small tail area with a dominating head group, while a large packing parameter reflects either a larger tail area or a small head group. Thus, highly curved aggregates (*e.g.* spheres) in water are attributed to small packing parameters, whereas aggregates with less curvature (*e.g.* vesicles or macroscopic bilayers) are attributed to large packing parameters (Fisher, 2000).
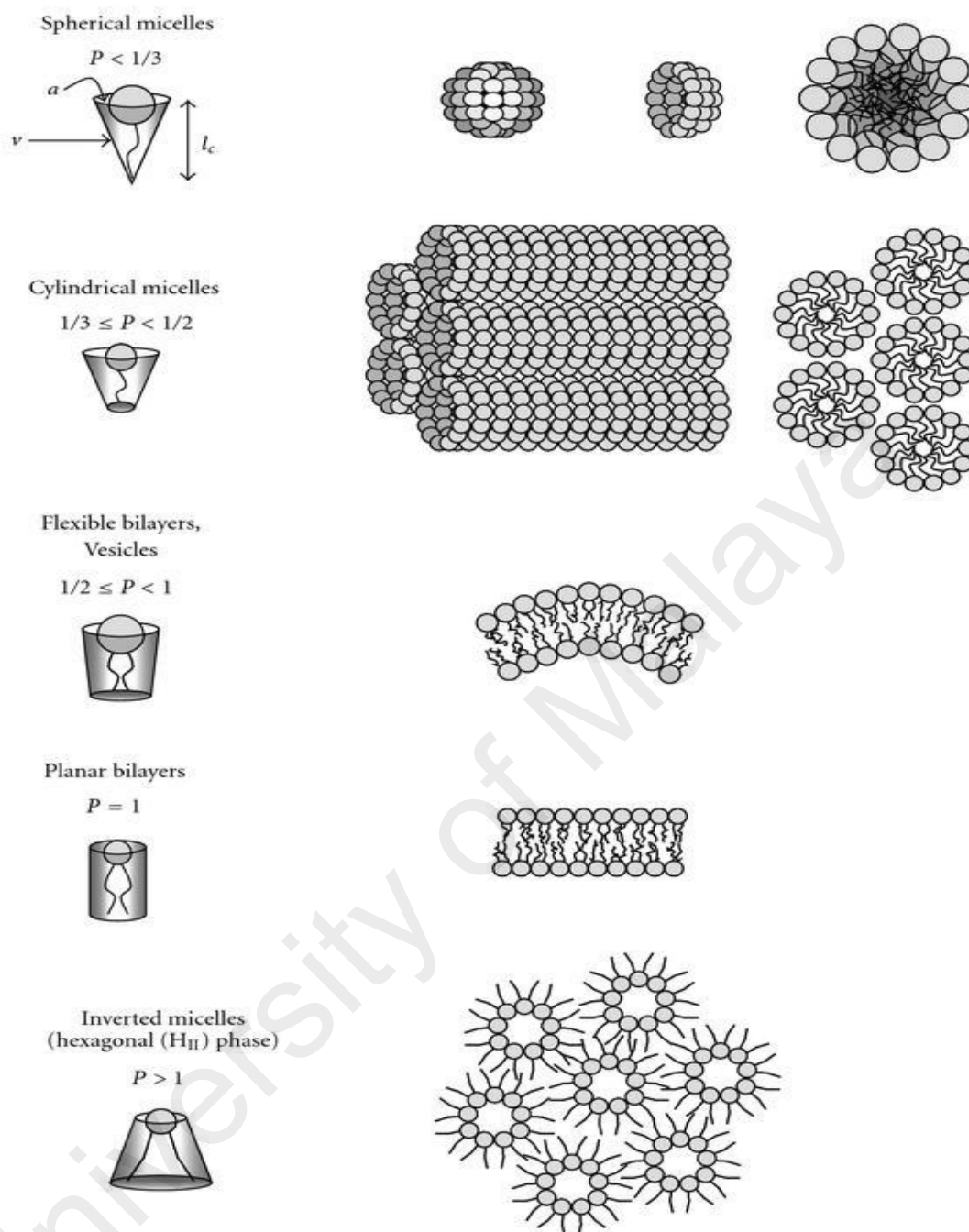
Figure 2.27: Packing parameter of a surfactant molecule and correlated assembly structures (Balazs & Godbey, 2011).

2.8.2 Liquid crystals

More than a century since the discovery of liquid crystal textures, analysis by polarizing microscopy has become a primary tool for the characterization and identification of different liquid crystalline phases. The molecules in a crystal are usually ordered in both position and orientation; this feature can be considered as the

main difference between a crystal and a liquid, in which neither positional nor orientation restrictions are applied. Liquid crystals do not exhibit positional order like a liquid. However, the orientation of molecules is not at random but reflects a more or less ordered system. The assembly of amphiphilic molecules in a solvent, *e.g.* surfactants in water, gives rise to liquid crystalline behaviour, if the assembly gets macroscopic, *i.e.* exceeds the size of a micelle (Rosen, 2004).

Lyotropic liquid crystals are frequently found in everyday life. For example, detergents are often formulated into liquid crystal phases to improve the washing performance (foam stabilization), butter for cooking often contains lyotropic liquid crystal phases and also the outermost layer of the skin and the biological membrane contain liquid crystal phases. In conclusion, lyotropic liquid crystals are essential for everyday human activities.

Amphiphilic molecules in the aqueous solution start to assemble in micelles (L_1-phase), and their geometric shape depends on the packing parameter of the individual surfactants. The viscosity of surfactant solutions increases because of the ordered molecular arrangement, particularly for larger assembly dimensions, which reflect the formation of liquid crystalline phases (Rosen, 2004). Spherical micelles can easily pack into a (discontinuous) cubic liquid crystal (I_1-phase). Hexagonal liquid crystals (H_1-phase) form upon close packing of cylindrical micelles, while disc-shaped micelles easily turn into lamellar liquid crystals ($L\alpha$-phase). The phases are displayed in Figure 2.28. In general, the surfactants with bulky head groups prefer the hexagonal phase, whereas surfactants with two hydrophobic chains favour the lamellar phase. The increase of the surfactant concentration changes the shape of a surfactant assembly, from spherical over cylindrical to lamellar. Hexagonal phases are usually encountered at lower surfactant concentration than lamellar phases. Some cylindrical micelles become

branched and interconnected with increasing surfactant concentration, thus leading to a bi-continuous liquid crystalline phase (V_1-phase) (Rosen & Kunjappu, 2012).
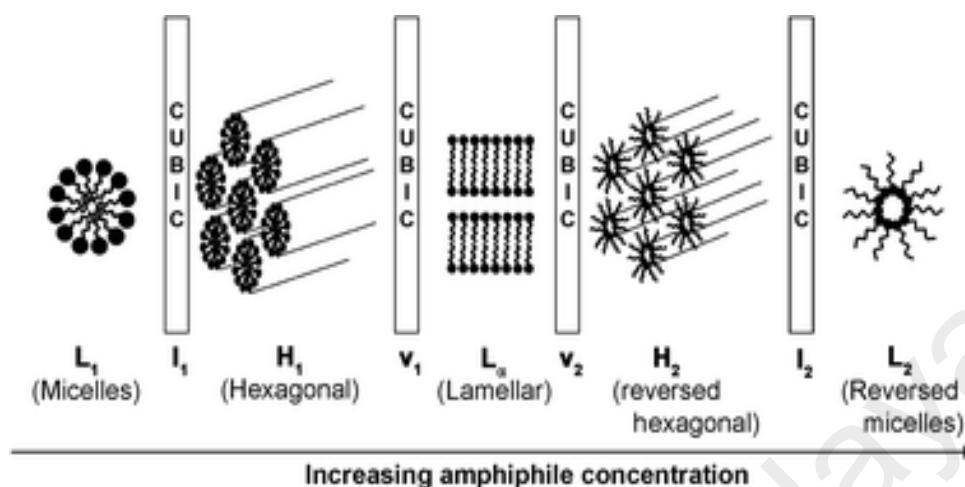
Figure 2.28: Assembly types of surfactants Micelles with cubic (I, V), hexagonal (H), and lamellar (Lα) liquid crystal structures (Kaasgaard & Drummond, 2006).

2.9 ENVIRONMENTAL EFFECTS AND SURFACTANT TOXICITY

Surfactants form the largest amount of synthetic chemicals worldwide. They are routinely deposited into the aqueous environment in diverse ways, either as part of an intended process or by various industrial applications and household wastes. Chemical and physicochemical processes are important sources of toxic substance emission into the marine environment (Emmanuel *et al.*, 2005).

Surfactants are found in wastewater discharges, sewage treatment plant effluents, surface and ground water, and sediments worldwide (Li, 2008). Cation surfactants are strongly sorbed by solid materials, particularly clay, whereas anionic surfactants are not appreciably sorbed by inorganic solid materials. Both anionic and non-ionic surfactants have significant sorption in activated sludge and organic sediments (*Canadian Water Quality Guidelines for the Protection of Aquatic Life: Glyphosate*, 2012). The toxicity of surfactants is indicated by the ability of the compounds to adsorb and penetrate the cell membrane of aquatic organisms (Li, 2008; Rosen, Li, Morrall, & Versteeg, 2001). The main reasons of surfactant toxicity on microorganisms are as follows: (*i*) the

interaction of the lipid component of the surfactant with microorganisms leads to the disruption of cellular membranes and loss of microbial contents to the exterior, (*ii*) protein reaction with the surfactant molecule is crucial to the cell function of microorganisms (Emmanuel *et al.*, 2005; Zhang, Li, Huang, & Thring, 2010). In addition, surfactants that are not toxic by itself can cause toxicity owing to the emulsification of highly toxic organic contaminants (Shin, Ahn, & Kim, 2005).

2.10 ILS BASED SURFACTANTS

The ability to self-organize in solutions opens additional perspectives of ILs applications in: chemical synthesis, catalysis, electrochemistry, extraction and chromatography, polymer materials synthesis, nanomaterials *etc.*, and many results obtained in the last years have supported this. Obviously, better understanding of self-assembly phenomena in solutions of ILs presents a challenging physicochemical task and helps in many applications.

Many ILs are amphiphilic substances with pronounced hydrophilic and lipophilic molecular fragments. This ILs phenomenon determines their surface activity and ability to self-organize in the individual state (pure form) and in solutions. Such properties have particularly been presented in dialkylimidazolium, dialkylpyridinium and alkylammonium salts which belong to the most widely applied ILs.

Self-organizing of dialkylimidazolium ILs was extensively studied experimenta- lly and by computer software simulations. Nano-structural organization of individual liquid 1-alkyl-3-methylimidazolium salts $[C_n mim]X$ (X denotes anion) with various alkyl chain length (various n value) was confirmed by molecular dynamic (MD) simulations (Canongia Lopes & Pádua, 2006; Jiang, Wang, & Voth, 2007; Wang & Voth, 2005). Positively charged imidazolium rings and anions arranged in three-dimensional polar network were revealed. These two types of molecular formation were supported by

strong electrostatic interactions whereas alkyl groups' aggregate to form nonpolar domains and the short-ranged van der Waals interactions are decisive.

Thus, micro-phase separation to hydrophilic and lipophilic regions is observed in ILs. MD simulations of 1-octyl-3-mehylimidazolium nitrate mixtures with water (Jiang *et al.*, 2007) have shown that with the increasing water content the polar network of IL ions will be ruined. Further, at high dilutions, the role of the interactions between water molecules and polar IL groups are increasing where the formation of micelles is registered in aqueous surrounding. It has been experimentally confirmed that in certain concentration range, long-chain ILs and water form liquid crystal ionomer gels (Firestone *et al.*, 2002; Firestone, Rickert, Seifert, & Dietz, 2004) as well as, the structures of lyotropic phases were studied for concentrated solutions of alkylimidazolium bromides (Goodchild *et al.*, 2007).

IL-type Gemini surfactants are a new class of surfactants having two hydrophobic tails and two hydrophilic head groups connected through linkage adjacent to the hydrophilic head groups in a molecule. They display greater propensity to form micelles and can efficiently reduce surface tension compared with their corresponding conventional single-chain surfactant counterparts (Ao, Xu, Zhu, & Bai, 2008; Manet, Karpichev, Bassani, Kiagus-Ahmad, & Oda, 2010; Matsuoka, Chiba, Yoshimura, & Takeuchi, 2011; Siddiqui, Khan, Khan, Dar, & Kabir ud, 2011; Sohrabi, Bazyari, & Hashemianzadeh, 2010; Zhao, Zhu, Li, Hu, & Cao, 2010). Compared with the conventional mono-chain surfactants, the interfacial activity of Gemini surfactants in aqueous solution is much greater, such as lower critical micelle concentration (CMC), higher adsorption efficiency, and better solubilizing, wetting, foaming, and lime-soap dispersing properties (Bell *et al.*, 2003; Zana, 2002; Zheng & Zhao, 2006). Therefore, they have promising applications in skin care, medicine, life science, petro-chemistry,

construction of porous materials, *etc.* (Badea, Wettig, Verrall, & Foldvari, 2007; Chen *et al.*, 2005; Han, Xu, Hou, Yu, & Wang, 2004).

The backbones of Gemini cationic IL surfactants are usually hydrophobic aliphatic or aromatic chains, whereas, the type of polar head-groups is versatile, such as imidazolium (Ao *et al.*, 2008; Kamboj, Singh, Bhadani, Kataria, & Kaur, 2012; Ren *et al.*, 2015), pyridinium (Mahajan, Mahajan, Bhadani, & Singh, 2012; Patial, Shaheen, & Ahmad, 2013), pyrrolidinium (Cai, Li, Yang, & Dong, 2012; Zou, Dong, Yang, & Li, 2015), piperidinum, (Menger, Keiper, & Azov, 2000), quaternary ammonium (Lu, Lan, Liu, Huang, & Wang, 2012; You, Wu, Zhao, Ye, & Zou, 2011; Zhou & Zhao, 2009), phosphonium (Bakshi, Singh, Singh, & Kaur, 2004; Kabir ud, Sharma, & Ajmal Koya, 2014). Unlike the backbone and head-groups, the spacers of gemini surfactants may be hydrophobic (Du, Lu, Li, Wang, & Yang, 2006; Payagala *et al.*, 2007; Zhu, Cheng, Chen, & Jiang, 2012) or hydrophilic (Bendjeriou, Derrien, Hartmann, Charnay, & Partyka, 2005; Liu *et al.*, 2010), therefore, they can be altered in a wide range. Types of backbones, head-groups and spacers are the main structural factors affecting the properties of Gemini surfactants.

The influence of the spacer structures on the properties of Gemini surfactants have been widely studied (Hajy Alimohammadi *et al.*, 2012; Parikh *et al.*, 2015; Wang & Marques, 2008; Zhang *et al.*, 2012; Zhu *et al.*, 2012), and it was found that the spacer plays an important role in the aggregation properties of Gemini surfactants. Generally, the ever-studied spacers might be divided into three categories. The first is the flexible spacer that might be hydrophobic saturated aliphatic chain of different length or hydrophilic polyethylene oxide chain (Du *et al.*, 2006; Liu *et al.*, 2010; Payagala *et al.*, 2007). This kind of spacer is employed more frequently in the syntheses of Gemini surfactants. The second is rigid spacer that contains only a benzene ring or an unsaturated bond (Zaijun, Rui, Zhongyun, & Fushan, 2005). The third is semi-rigid

spacer that contains both the rigid and flexible groups (Menger *et al.*, 2000; Zhu *et al.*, 2012). In the semi-rigid spacer only one benzene ring, double or triple bond has been used as the rigid group. It is clear that in the ever-reported rigid and semi-rigid spacers, the rigid moiety is usually short.

For example, cationic Gemini surfactants with big imidazolium head groups as reverse-micelle system showed a significantly stronger tendency toward self-aggregation comparing to other types of cationic head-groups (Ao *et al.*, 2008; Paul & Mitra, 2005). The biological applications of imidazolium Gemini surfactants are attributed to the strong attraction between imidazolium head groups and aromatic rings through π–π interaction (Fry, 2003; Xia, Yu, Jiang, Mahmood, & Liu, 2007). These strong attractions between the imidazolium ring and co-surfactants facilitate the immobilization of the (W/O) interface and form the compact membranes. According to the distinct polarizability of imidazolium head groups, they could be used as supramolecular templates in the preparation of functional materials (Kuang, Brezesinski, & Smarsly, 2004; Zhou & Antonietti, 2004); or may be applied to modify various types of chemical reactions such as: nucleophilic substitutions, decarboxylation, and cyclization as reported (Ao *et al.*, 2008).

In comparison with classical molecular fluids, the atomic force microscopy studies of ILs in contact with solids, have shown that the supra-molecular structuring is observed in the bulk liquid as well as layers adjacent to the solid surface, where the long-range order appears (Hayes, Warr, & Atkin, 2010). Specific behaviour of systems containing ILs is dependent on the complex character of intermolecular interactions incorporating many constituents; ion-ion, van der Waals, dispersion interactions, hydrogen bonding besides n–π and π–π-interactions in many systems. Intermolecular interactions and self-organization in ILs could be affected by varying the chemical structure of ions which is important for many applications of ILs.

Micellar solutions of classical ILs surfactants have gained a huge attention (Inoue, Higuchi, & Misono, 2009; Li, Zhang, Zheng, & Inoue, 2009; Li *et al.*, 2008). Due to the fact that an aggregate surfactant could dissolve various kinds of substances that are not soluble in ILs, the adding surfactants will extend the range of ILs applications. In particular, micellization of alkylimidazolium ILs in aqueous solutions has intensively been studied intensively since 2004, where ILs act as surface active solutes (Blesic *et al.*, 2008; Blesic *et al.*, 2007; Dong, Li, Zheng, Yu, & Inoue, 2007; Łuczak, Jungnickel, Joskowska, Thöming, & Hupka, 2009; Smirnova *et al.*, 2009). The studies allowed comparing the obtained aggregation information of many individual ILs and their mixtures in solutions with classical surfactants. Chiral and long-chain imidazolium ILs ($[C_{16}mim]Cl$ and others) are superior in comparison with classical surfactants such as CTAC and CTAB (cetyltrimethylammonium chloride and bromide, respectively) which are widely applied as templates in sol-gel technology. The preferences can be attributed to the long ordering effect of the imidazolium polar groups system comparing with ammonium ions (Smirnova & Safonova, 2010).

In particular, disc-like imidazolium head groups have a tendency to arrange themselves in a parallel fashion, and such ordering is supported by a distinct polariza-bility of the groups and by the hydrogen bonding. As a result, when ILs are used as templates, meso-structures with a low curvature such as lamellar and bi-continuous cubic phases are formed preferentially. A method to synthesize zeolite analogues is proposed where imidazolium ILs perform both as a solvent and as a template (Cooper *et al.*, 2004).

2.11 BIODEGRADABLE SURFACTANTS

Many studies have been published reporting the biodegradation of plastics, polymers (Ali Shah, Hasan, Shah, Kanwal, & Zeb, 2013; Eubeler, Bernhard, & Knepper, 2010; Sinha Ray, 2013; Way, Wu, Dean, & Palombo, 2010) and especially

surfactants (Hirata *et al.*, 2009; Pisárčik, Polakovičová, Pupák, Devínsky, & Lacko, 2009; Sayed *et al.*, 2012). Boethling presented the design of linear alkyl-benzene sulfonates and dialkyl quaternaries as biodegradable surfactants. Two case studies were carried out highlighting the importance of designing biodegradable chemicals as one way to reduce pollution at the source (Boethling, 1994). Due to close structural similarity of many ILs and surfactants, the factors that improved the biodegradation of surfactants may be applicable to IL.

Linear alkyl sulfonates were developed as biodegradable alternatives to tetra-propylene alkyl-benzene sulfonates. By reducing the branching in the alkyl side chain of the surfactant, β-oxidation of the hydrocarbon chain is promoted, with the result that linear alkyl sulfonates are almost completely biodegraded in sludge plants treatment (Mungray & Kumar, 2009; Temmink & Klapwijk, 2004). Generally, ILs with branched hydrocarbon side chains are rare (Erdmenger, Vitz, Wiesbrock, & Schubert, 2008). The majority of the prepared novel ILs contain linear hydrocarbon side chains, where the introduction of branching into side chains should be avoided. Toxicity, ecotoxicity, biodegradation and bioaccumulation data should be collected as a priority for these compounds due to their potential to persist in the environment.

Quaternary ammonium compounds first gained prominence over 70 years ago. The biocidal properties of simple quaternary ammonium salts were significantly enhanced by the presence of a long alkyl group (García, Campos, Sanchez-Leal, & Ribosa, 1999; You *et al.*, 2011). Up to the 1990's three classes of quaternary ammonium compounds dominated the high volume fabric softeners market: dialkyl dimethyl ammonium salts, imidazolium quaternary ammonium salts and ethoxylated ethanaminium quaternary ammonium salts. They were replaced by surfactants containing incorporation of hydrolysable bonds like amide or ester which led to new biodegradable quaternary ammonium surfactants (Boethling, 1994).

The presence of linear hydrocarbon chains included esters or amides as hydrolysable site, has dominated the early studies to prepare biodegradable ILs. However, the length of the side chains is a major difference in the structure of surfactants against ILs.

CHAPTER 3: SYNTHESIS AND ANTIBACTERIAL EVALUATION OF SOME NOVEL IMIDAZOLE AND BENZIMIDAZOLE SULPHONAMIDES

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(2a, 3a, 4a) X= CH₃

(2b, 3b, 4b) X= OCH₃

(2c, 3c, 4c) X=NO₂
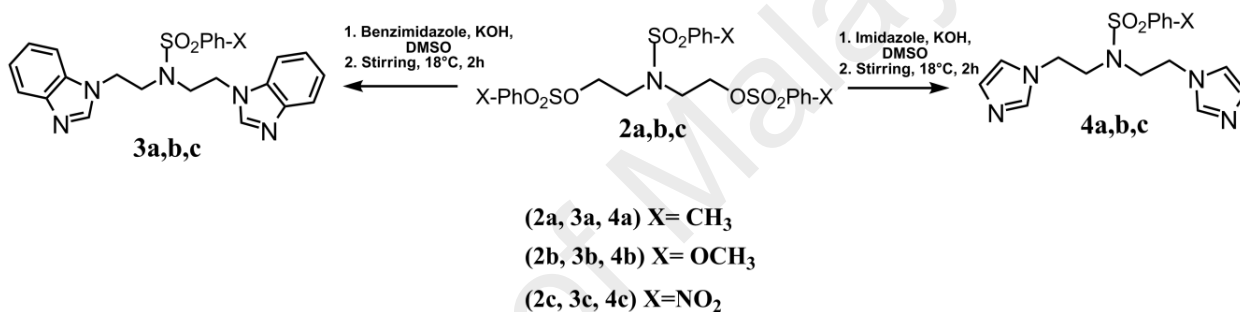
3.1 INTRODUCTION

Heterocycles containing sulphonamide moieties have attracted obvious attention due to their significant biological properties and their role as pharmacophores (Akurathi *et al.*, 2010; Andrighetti-Fröhner *et al.*, 2009; Chandak, Bhardwaj, Sharma, & Sharma, 2013; Kamal *et al.*, 2013; Lu *et al.*, 2011; Luo *et al.*, 2011). Studies have shown that sulphonamide compounds were used as antibacterial agents (Azab, Youssef, & El-Bordany, 2013; Ezabadi *et al.*, 2008; Gadad, Mahajanshetti, Nimbalkar, & Raichurkar, 2000), anticancer (Bano *et al.*, 2011; Ghorab, Ragab, & Hamed, 2009; Ghorab, Ragab, Heiba, Arafa, & El-Hossary, 2010), anti-inflammatory, analgesic agents (El-Araby, Omar, Hassanein, El-Helby, & Abdel-Rahman, 2012; Nanthakumar, Muthumani, & Girija; Sondhi *et al.*, 2000), antifungal agents (Ezabadi *et al.*, 2008; Zoumpoulakis *et al.*, 2012) and antiviral agents (Chen *et al.*, 2010). Imidazole and its derivatives have been reported to be bioactive molecules in many important biological systems with a wide range of pharmacological activities. In general, they are well known as proton donors and/or acceptors in enzymatic systems, coordination system ligands and as the basis of charge–transfer processes (Atia, 2009; Kipp, Faraj, Li, & Njus, 2004), as well as antibacterial (González-Chávez, Méndez, Martínez, Pérez-González, & Martínez-Gutiérrez, 2010; Jain, Ravichandran, Sisodiya, & Agrawal, 2010; Khalafi-Nezhad, Soltani Rad, Mohabatkar, Asrari, & Hemmateenejad, 2005), anti-parasitic (Hernández-Núñez *et al.*, 2009), antiepileptic (Karakurt *et al.*, 2001), anti-inflammatory and anticancer agents (Bhatnagar, Sharma, & Kumar N., 2011; Suzuki *et al.*, 1992; Vijesh, Isloor, Telkar, Arulmoli, & Fun, 2013).

In our study, new promising bioactive compounds based on the sulphonamide moiety were designed and synthesized by a simple and efficient method, followed by the evaluation of their biological activities. The synthesis emphasizes a strategy that combines two or more pharmacologically compatible moieties in one molecule by

attaching a sulphonamide moiety to an imidazole, benzimidazole or another sulphonamide moiety. We believe this route has a wide range of applications and we have high expectations for the future development of new compounds.

3.2 RESULTS AND DISCUSSION

3.2.1 Synthesis

Bis-benzimidazole and bis-imidazole sulphonamides were synthesized from the diol **1** as shown in Figure 3.1.

(2a, 3a, 4a) X= CH$_3$
(2b, 3b, 4b) X= OCH$_3$
(2c, 3c, 4c) X=NO$_2$
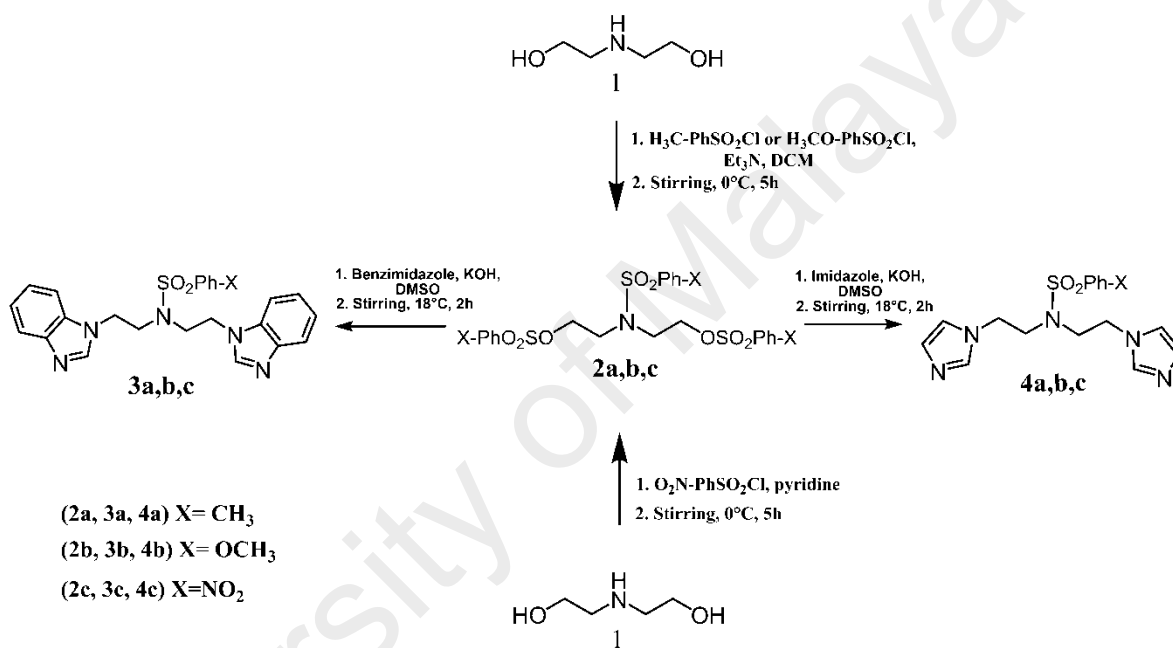
Figure 3.1: Synthesis of bis-benzimidazole and bis-imidazole sulphonamides **3a–c**, **4a–c**.

Three bis-benzimidazole sulphonamides and three bis-imidazole sulphonamides compounds were obtained by treating imidazole (or benzimidazole) with tris-(4-substituted benzensulphonate)-diethanolamine under basic conditions to form the corresponding bis-imidazole (or bis-benzimidazole) sulphonamides. The reaction of tris-(4-substituted benzensulphonate) with either imidazole or benzimidazole has produced symmetrical products and it is in agreement with literature (Chak & McAuley, 2006) to synthesize tris-(4-substituted benzensulphonate)-diethanolamine. In the current study, these intermediate states (*i.e.* compounds **2a-c**) were applied as reagents to

synthesize symmetric bis-imidazole (or bis-benzimidazole) sulphonamide compounds. The proton abstraction from the nitrogen of imidazoles rings by potassium hydroxide (Starikova *et al.*, 2003) is considered the key step in this reaction. The resulting imidazolide (or benzimidazolide) anions will attack the carbon bearing the 4-substituted benzensulphonate in both sides of diethanolamine with the nitrogen atom which is protected via the third 4-substituted benzenesulphonyl group.

The FTIR spectra for compounds **3a–c** and **4a–c** showed absorption bands at 1,350–1,375 cm^{-1} and 1,150–1,185 cm^{-1} which were assigned to the O=S=O group. The same compounds displayed stretching absorption bands at 3,100–3,047 cm^{-1}, 2,975–2,855 cm^{-1}, 1,590–1,457 cm^{-1}, and 1,666–1,584 cm^{-1} attributed to (C-H)$_{Aromatic}$, (C-H)$_{Aliphatic}$, (C=C)$_{Aromatic}$, and (C=N), respectively. The target compounds **3b** and **4b** showed characteristic stretching absorption bands at 1,220 cm^{-1} and 1,238 cm^{-1} which were assigned to C-O-C, while the bands at 1,529–1520 cm^{-1} and 1,355–1,340 cm^{-1} for compounds **3c** and **4c** were assigned to Ar-NO$_2$.

The ^{1}H-NMR spectra of compounds **3a**, **4a**, **3b**, and **4b** showed singlets at δ 2.33 ppm and δ 2.80 ppm which were assigned to the 4-methyl and 4-methoxy protons of the aryl-sulphonyl groups, respectively. A triplet recorded at δ 3.31–3.54 ppm and δ 3.95–4.27 ppm was assigned to the protons of four methylene groups of compounds **3a–c** and **4a–c**. The aromatic protons of compounds **3a–c** and **4a–c** were recorded as multiplets in the δ 6.89–7.83 ppm range. A singlet which was observed at δ 7.42–8.16 ppm corresponds to the isolated C-H of the imidazole and benzimidazole rings. The ^{13}C-NMR spectra of compounds **3a–c** and **4a–c** showed characteristic peaks in the δ 163.23–163.34 ppm, δ 149.03–153.12 ppm and δ 129.78–144.28 ppm ranges which were assigned to C$_{Ar}$-O, C$_{Ar}$-NO$_2$ and C$_{Ar}$-S, respectively. The peaks recorded at δ 43.09–45.77 ppm, δ 48.20–50.37 ppm and δ 56.18–56.24 ppm were attributed to the methylene and methoxy carbon atoms, correspondingly.

The mass spectra of compounds **3a** and **4a** showed various characteristic peaks. Those at *m/z* 459.2 and 359.1 were assigned to the molecular ions of **3a** and **4a**, respectively. The base peak of **3a** at *m/z* 328.1 was assigned to the *N*-(benzimidazol-1-yl)ethyl-*N*-4-dimethylbenzenesulphonamido radical, while the base peak of **4a** at *m/z* 278.1 was assigned to the *N*-(imidazole-1-yl)ethyl-(4-methylbenzene) sulphonamide-methyliumyl ion. The characteristic peaks at *m/z* 155.0 and 91.0 for both **3a** and **4a** were due to (4-methylphenyl)dioxosulphanium and 4-methylbenzene-1-ylium ions, respectively, Figures 3.2 and 3.3 show the fragmentation patterns for **3a** and **4a**, respectively.
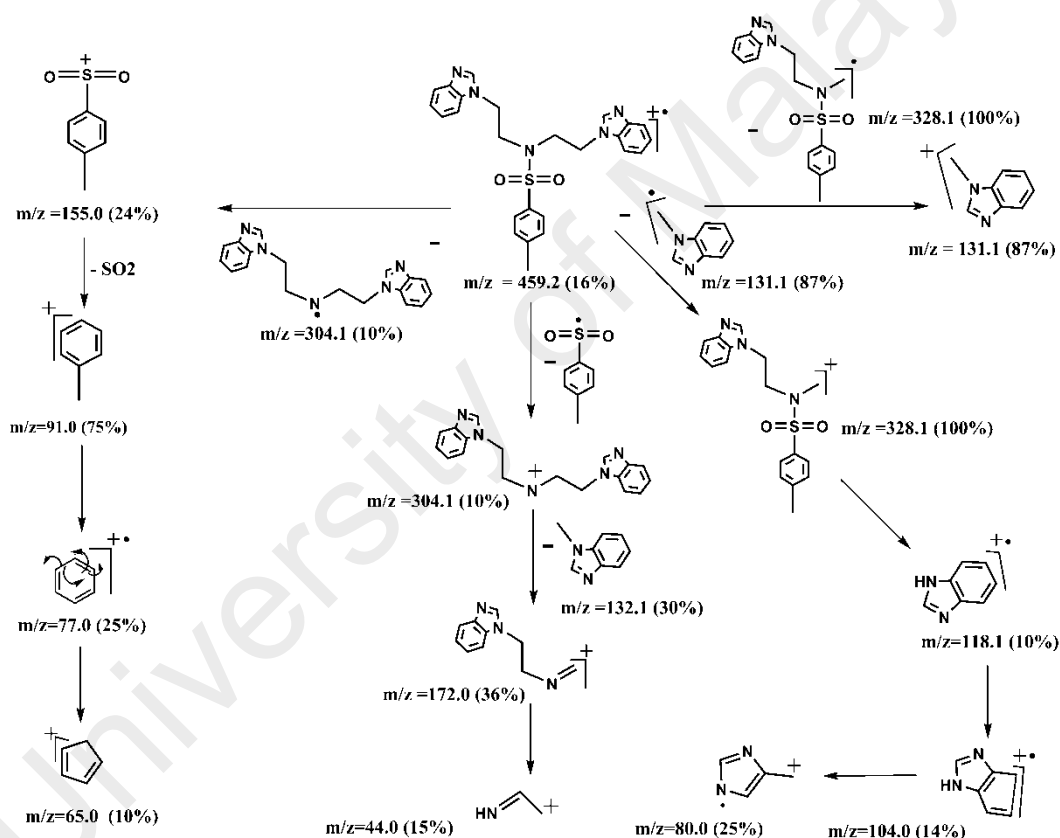
Figure 3.2: Mass fragmentation pattern of 3a.

Figure 3.3: Mass fragmentation pattern of 4a.

Figure 3.4 shows the preparation of compounds **9** from 2-((benzimidazol-2-yl) methylthio)-benzimidazole. A simple method was adopted to synthesize a pure heterocyclic product in good yield. 2-Mercaptobenzimidazole and sodium methoxide were stirred with 2-chloromethylbenzimidazole. A pale-yellow solid precipitated instantly due to the reactivity of -SH group then it was treated with tosyl chloride in pyridine.

Figure 3.4: Synthesis of *N*-4-methylbenzenesulphonyl ((*N*-(4-methylbenzenesulph-
onyl)-benzimidazol-2-yl)methylthio)-benzimidazole **(9)**.

The infrared spectrum of compound **8** indicated the absence of a free -SH absorption band and the appearance of S-C stretching at 748 cm^{-1}, while the absorption bands at 1,365 and 1,170 cm^{-1} were assigned to the O=S=O group in compound **9**. The ^{1}H-NMR spectrum of compound **9** showed two singlet peaks at δ 2.31, and 2.37 ppm integrating for six protons for the two methyl protons of the sulphonamido moieties. The protons of the methylene group appeared as a singlet at δ 5.18 ppm, whereas the aromatic protons appeared as multiplets and doublet peaks in the δ 7.19–7.98 ppm range. The ^{13}C-NMR of compound **9** showed peaks at δ 21.77 and 21.80 ppm which was assigned to two non-corresponding methyls for two tosyl groups. The $\underline{C}$H$_2$-S carbon atom was observed at δ 31.20 ppm.

Figure 3.5 shows the preparation of compound **11** from 2,2′-(ethylenedioxy)bis-(ethylamine) by treating with tosyl chloride and triethylamine in dry dichloromethane that produced a significant yield of pure bis-sulphonamide compound **11**.
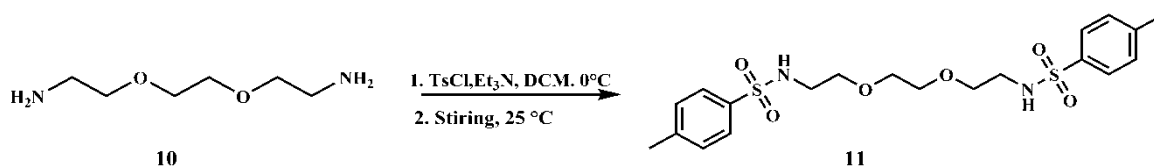
Figure 3.5: Synthesis of 4-methyl-*N*-(2-{2-[2-(4-methylbenzenesulphonamide)-ethoxy]ethoxy}ethyl)-benzenesulphonamide (11).

The FTIR spectrum for compound **11** showed absorption bands at 3,276 cm^{-1} indicating the presence of a N-H group, 1,088 cm^{-1} for a C-O-C group, 1,124 cm^{-1} for C-C-O vibrations, and the peaks at 1,317, 1,152 cm^{-1} were assigned to the O=S=O group. The ^{1}H-NMR spectrum of compound **11** showed characteristic doublet peaks at δ 7.27 ppm and 7.73 ppm which were assigned to the aromatic protons. The methylene groups were recorded as a quartet at δ 3.09 ppm and a triplet at δ 3.50 ppm integrating for eight and four protons, respectively. The amino protons of compound **11** appeared as a triplet at δ 5.50 ppm. The corresponding methyls for two tosyl groups were observed as a single peak at δ 2.39 ppm integrating for six protons. The ^{13}C-NMR of compound **11** showed aromatic carbon peaks at δ 143.45, 137.07, 129.78 and 127.18 ppm. The peak at δ 21.59 ppm was assigned to the two corresponding methyl groups while, peaks of $4 \times \underline{C}H_2$-O were observed at δ 69.78 and 70.43 ppm. The structures of compounds **3a**, **4a**, **9** and **11** were further characterized by single crystal X-ray diffraction which indicated tetragonal and triclinic crystal systems for **3a** and **4a**, respectively, while the crystal structures of **9** and **11** have been reported (Al-Mohammed, Alias, Abdullah, & Khaledi, 2011, 2012). Crystallographic data for compounds **3a** and **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 923664 and CCDC 923665, respectively. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)-1223-336-033; or [e-mail: deposit@ccdc.cam.ac.uk].

3.2.2 Antibacterial Activities

In an *in vitro* antibacterial bioassay, the eight compounds **3a–c**, **4a–c**, **9** and **11** were evaluated by microbroth dilution assays using representative standard strains of Gram-positive and Gram-negative bacteria, and the results are listed in Table 3.1. Minimum inhibitory concentrations (mg/mL) of the compounds against the test microorganisms were determined. It was shown (Figure 3.6) that the majority of the compounds studied possessed significant antibacterial activity towards most of the selected microorganisms. The highest activities were observed for compounds **9** and **11**, followed by **3c** and **4c** then **3b** and **4b**. Compounds **3a** and **4a** showed the least antibacterial activity for the selected concentration range, as shown in Figure 3.6. In the structure-activity relationship (SAR) studies, it has been reported that the incorporation of two different pharmacophores in a single structure enhanced the resulting compounds' biological activities (Gu *et al.*, 2012; Kossakowski, Krawiecka, Kuran, Stefańska, & Wolska, 2010; Plech, Wujec, Siwek, Kosikowska, & Malm, 2011). The presence of substituents on aromatic rings also affects the antibacterial activities of the compounds. Compounds with resonance electron-withdrawing substitution (nitro) showed greater antibacterial activities than those with electron-donating substituent groups (methyl and methoxy) (Gu *et al.*, 2012; Kossakowski *et al.*, 2010; Plech *et al.*, 2011) and this is clearly shown in the case of compounds **3a–c** and **4a–c**. Studies have also shown that the presence of a sulphur atom as a sulphide in drugs provides a greater stability to three-dimensional structure of the molecule (Cecil, 1963). It was observed that the presence of sulphur in compound **9** has a significant contribution to the antibacterial activities against Gram-positive and Gram-negative bacteria. This is believed due to the existence of a toxophoric (-N=C-S-) group (Alwan, 2012; Mamolo, Falagiani, Zampieri, Vio, & Banfi, 2001; Mazzone *et al.*, 1982). Furthermore, the attachment of two toxophoric groups (amine) with benzenesulphonyl moieties in compound **11** enhanced the antibacterial

activity against most of both kinds of bacteria (Greim, Bury, Klimisch, Oeben-Negele, & Ziegler-Skylakakis, 1998; Matos *et al.*, 2013; Ouyang *et al.*, 2012).

It is obvious from the overall antibacterial results that different compounds reacted in different ways against bacteria. In these compounds, strains of Gram-positive bacteria seem to be more sensitive than Gram-negative micro-organisms.

Table 3.1: Antibacterial activities of compounds studied.
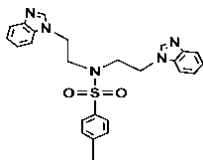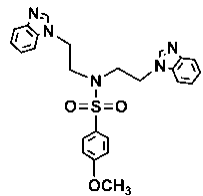
No.	Structure of samples	Bacteria/MICs (mg/mL)									
		Gram-negative bacteria				*Gram-positive bacteria*					
		Escherichia coli	*Salmonella typhimurium*	*Pseudomonas aeruginosa*	*Acinetobacter calcoaceticus*	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Bacillus subtilis*	*Rodococcus ruber*	*Enterococcus faecalis*	*Staphylococcus epidermidis*
3a		>0.5	0.30	>0.5	>0.5	0.30	0.25	0.30	0.40	0.35	0.30
3b		0.2	>0.5	>0.5	0.15	0.30	0.30	0.40	0.15	0.10	>0.5

Table 3.1: *Cont.*
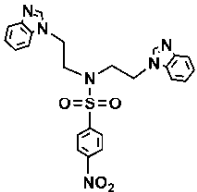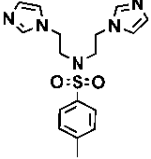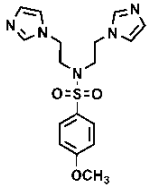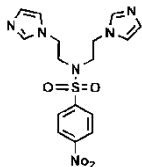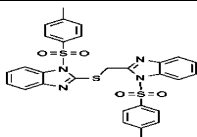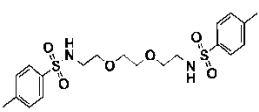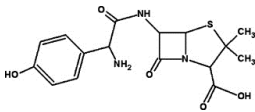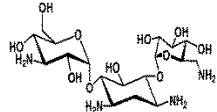
No.	Structure of samples	Bacteria/MICs (mg/mL)									
		Gram-negative bacteria				*Gram-positive bacteria*					
		Escherichia coli	*Salmonella typhimurium*	*Pseudomonas aeruginosa*	*Acinetobacter calcoaceticus*	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Bacillus subtilis*	*Rodococcus ruber*	*Enterococcus faecalis*	*Staphylococcus epidermidis*
3c		0.40	0.05	0.20	0.05	0.10	0.05	0.40	0.40	>0.5	0.20
4a		>0.5	0.30	>0.5	>0.5	0.20	0.20	0.40	0.40	0.30	0.40
4b		0.05	0.15	0.30	>0.5	0.40	0.10	0.10	0.30	0.35	>0.5

Table 3.1: *Cont.*

No.	Structure of samples	Bacteria/MICs (mg/mL)									
		Gram-negative bacteria				Gram-positive bacteria					
		Escherichia coli	*Salmonella typhimurium*	*Pseudomonas aeruginosa*	*Acinetobacter calcoaceticus*	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Bacillus subtilis*	*Rodococcus ruber*	*Enterococcus faecalis*	*Staphylococcus epidermidis*
4c		>0.5	0.30	>0.5	0.30	0.10	0.15	0.30	0.40	>0.5	0.30
9		>0.5	>0.5	0.30	0.30	0.05	0.10	0.05	0.05	>0.5	0.15
11		0.40	0.35	>0.5	>0.5	0.20	0.15	0.05	0.20	0.20	0.05

Table 3.1: *Cont.*

No.	Structure of samples	Bacteria/MICs (mg/mL)									
		Gram-negative bacteria				*Gram-negative bacteria*					
		Escherichia coli	*Salmonella typhimurium*	*Pseudomonas aeruginosa*	*Acinetobacter calcoaceticus*	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Bacillus subtilis*	*Rodococcus ruber*	*Enterococcus faecalis*	*Staphylococcus epidermidis*
AM		<0.05	<0.05	Nd	0.15	0.05	<0.05	0.25	<0.05	<0.05	nd
KA		<0.05	<0.05	<0.05	>0.5	<0.05	<0.05	<0.05	<0.05	>0.5	<0.05

MIC: Minimum inhibitory concentration, AM: Amoxicillin, KA: Kanamycin, nd: not detected.

Figure 3.6: MIC's Histogram for synthesized compounds (0.05–0.40 mg/mL concentration) versus ten strains of bacteria.

Thus, comparing the results of both the synthesized compounds and amoxicillin against *β*-lactam resistant Gram-positive bacteria (*Staphylococcus epidermidis*) demonstrated interesting antibacterial inhibitory values for most of the synthesized compounds. The MIC values are between 0.05 mg/mL (for compound **11**) to 0.4 mg/mL (for compound **4a**) whereas the *β*-lactam antibiotic amoxicillin was inactive against this strain of Gram-positive bacteria.

In addition, compounds **3c**, **4b**, and **9** showed significant activities, with MIC values (0.2, 0.3 and 0.3 mg/mL, respectively) toward a *β*-lactam resistant Gram-negative bacterium (*Pseudomonas aeruginosa*) when compared to the antibiotic amoxicillin. Compounds **4b**, **9** and **11** with MIC values of 0.10, 0.05 and 0.05 mg/mL, respectively showed interesting antibacterial activities against *Bacillus subtilis*, which required a high dose of amoxicillin (0.25 mg/mL) (Daniel, Harry, & Mai, 2012). Compounds **3a–b**, **4a–4b**, and **11** demonstrated inhibitory effects ranging between 0.1–0.35 mg/mL against the Gram-positive bacterium *Enterococcus faecalis*, however, the antibiotic kanamycin was inactive toward the samples at the concentration range of this study (0.05–0.5 mg/mL). Both commercial antibiotics amoxicillin and kanamycin exhibited MIC values (0.15 mg/mL and >0.5 mg/mL, sequentially) against *Acinetobacter calcoaceticus*, while

compound **3c** exhibited a significant antibacterial inhibitory effect at 0.05 mg/mL against the mentioned Gram-negative bacteria.

3.3 EXPERIMENTAL

3.3.1 General

The IR spectra were obtained by a Perkin Elmer 400 Fourier Transform Infrared (FTIR) spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on Jeol Lambda and ECA DELTA spectrometers at 400 MHz. The mass spectra were obtained using an Agilent 5975 system for EI/MS and a Finnigan TSQ7000 for HREI/MS (NUS, Singapore). Melting points were measured on a Gallenkamp melting point apparatus in open-end capillary tubes and are uncorrected. Thin layer chromatography was carried out on pre-coated silica gel plates (0.25 mm, 20 × 20 cm, 60F$_{254}$, E. Merck). Flash column chromatography was carried out on Silica Gel 60 (230–400 mesh, E. Merck). General grade solvents and reagents were purchased from commercial suppliers and used without further purification.

3.3.2 Synthesis *N*-(4-Methylbenzenesulphonyl)-bis((4-methylbenzensulphonyl(oxy))-ethyl)amine (2a) and *N*-(4-Methoxybenzenesulphonyl)-bis((4-methoxybenze-nesulphonyl(oxy))ethyl)amine (2b)

The compounds **2a** and **2b** were prepared according to the modified procedure described in (Chak & McAuley, 2006). Diethanolamine (5.5 g, 0.0524 mol) was dissolved in distilled dichloromethane (100 mL). The solution was cooled to 0 °C and then triethylamine (24.4 mL, 17.78 g, 0.176 mol) was added. With the temperature maintained at 0 °C, solid *p*-toluenesulphonyl chloride (31.4 g, 0.164 mol) or (4-methoxybenzenesulphonyl chloride (34.1 g, 0.165 mol) were added in portions with vigorous stirring over the course of 5 h to obtain compounds **2a** or **2b**, respectively. The reaction mixture was stirred at room temperature overnight. A pale yellow filtrate was produced from Et$_3$NHCl filtration, washed three times with 1 mol/L HCl, followed by 5 × 40 mL portions of water and 5 × 40 mL portions of saturated NaHCO$_3$ solution. The

organic layer was dried over anhydrous magnesium sulphate and evaporated to obtain yellow viscous liquid that solidified after 5–7 days.

3.3.2.1 *N*-(4-Methylbenzenesulphonyl)-bis((4-methylbenzenesulphonyl(oxy))ethyl)-amine (2a)

White solid; Yield: (87%) ; m.p. 98–100 °C; FTIR (cm^{-1}): 3,098, 3,045 (C-H)$_{Ar}$, 2,967 (C-H)$_{Aliph}$, 1,498, 1,472 (C=C)$_{Ar}$, 1,360, 1,155 (O=S=O); ^{1}H-NMR (CDCl$_3$) δ ppm: 7.77–7.65 (m, 6H, Ar-H), 7.54–7.48 (m, 4H, Ar-H), 7.44–7.40 (m, 2H, Ar-H), 4.45 (t, *J* = 6.23 Hz, 4H, CH$_2$-OTs), 3.23 (t, *J* = 6.23 Hz, 4H, CH$_2$-N-Ts), 2.33 (two singlets, 9H, Ar-CH$_3$). ^{13}C-NMR (CDCl$_3$) δ ppm: 144.60 (2 × C$_{Ar}$-S-O), 142.92 (C$_{Ar}$-S-N), 140.22 (2 × C$_{Ar}$-CH$_3$), 138.55 (C$_{Ar}$-CH$_3$), 131.04 (4 × CH$_{Ar}$), 129.40 (2 × CH$_{Ar}$), 127.23 (4 × CH$_{Ar}$), 127.10 (2 × CH$_{Ar}$), 55.79 (2 × CH$_2$-OTs), 46.66 (2 × CH$_2$-N-Ts), 22.30 (2 × CH$_3$-Ar), 20.52 (CH$_3$-Ar).

3.3.2.2. *N*-(4-Methoxybenzenesulphonyl)-bis((4-methoxybenzenesulphonyl(oxy))ethyl)amine (2b)

Off-white solid; Yield: 92%; m.p 157–158 °C; FTIR (cm^{-1}): 3,096, 3,050 (C-H)$_{Ar}$, 2,922 (C-H)$_{Aliph}$, 1,494, 1,466 (C=C)$_{Ar}$, 1,366, 1,160 (O=S=O), 1,220 (C-O-C); ^{1}H-NMR (DMSO-d_6) δ ppm: 7.80–7.76 (m, 4H, Ar-H), 7.65–7.51 (m, 2H, Ar-H), 7.19–7.16 (m, 4H, Ar-H), 7.06–7.04 (m, 2H, Ar-H), 3.98 (t, *J* = 5.77 Hz, 4H, CH$_2$-OTs), 3.28 (t, *J* = 5.77 Hz, 4H, CH$_2$-N-Ts), 3.85 (two singlets, 9H, Ar-O-CH$_3$); ^{13}C-NMR (DMSO-d_6) δ ppm: 164.18 (2 × C$_{Ar}$-OCH$_3$), 163.30 (C$_{Ar}$-OCH$_3$), 130.48 (4 × CH$_{Ar}$), 129.94 (C$_{Ar}$-S-O), 129.73 (2 × CH$_{Ar}$), 127.58 (2 × CH$_{Ar}$), 126.62 (2 × C$_{Ar}$-S-O), 115.50 (4 × CH$_{Ar}$), 115.13 (2 × CH$_{Ar}$), 68.51 (2 × CH$_2$-OTs), 56.41, 56.25 (3 × OCH$_3$), 47.80 (2 × CH$_2$-N-Ts).

3.3.3 Synthesis *N*-(4-Nitrobenzenesulphonyl)-bis((4-nitrobenzenesulphonyl(oxy))-ethyl) amine (2c)

A solution of 4-nitrobenzenesulphonyl chloride (21 g, 0.095 mol) in pyridine (40 mL) was added drop-wise to a solution of diethanolamine (3.5 g, 0.03 mol) in pyridine

(10 mL) while maintaining the temperature at 0 °C. The mixture was stirred at room temperature overnight and then poured into a beaker containing 400 mL of ice water. The mixture was then stirred for another 30 minutes, extracted with dichloromethane and washed with distilled water (3 × 50 mL). The organic layer was dried with anhydrous magnesium sulphate and the solvent evaporated under reduced pressure to give a green viscous liquid which solidified after five days to give a greenish-brown solid; Yield: 57%; m.p 184–186 °C; FTIR (cm^{-1}): 3,095, 3,048 (C-H)$_{Ar}$, 2,950 (C-H)$_{Aliph}$, 1,518, 1,476 (C=C)$_{Ar}$, 1,360, 1,174 (O=S=O), 1,532, 1,347 (Ar-NO$_2$); ^{1}H-NMR (DMSO-d_6) δ ppm: 8.43–8.39 (m, 4H, Ar-H), 8.35–8.32 (m, 2H, Ar-H), 8.14–7.11 (m, 6H, Ar-H), 3.55 (t, J = 6.25 Hz, 4H, CH$_2$-OTs), 3.32 (t, J = 6.25 Hz, 4H, CH$_2$-N-Ts); ^{13}C-NMR (DMSO-d_6) δ ppm: 159.20 (2 × C$_{Ar}$-NO$_2$), 158.78 (2 × C$_{Ar}$-S-O), 149.08 (CH$_{Ar}$-NO$_2$), 141.23 (C$_{Ar}$-S-O), 130.88 (4 × CH$_{Ar}$), 127.30 (2 × CH$_{Ar}$), 125.43 (4 × CH$_{Ar}$), 123.84 (2 × CH$_{Ar}$), 63.53 (2 × CH$_2$-OTs), 53.44 (2 × CH$_2$-N-Ts).

3.3.4 General Procedure for Synthesis of 3a, 3b, 3c and 4a, 4b, 4c

Potassium hydroxide (1.85 g, 0.033 mol) was added to a solution of imidazole or benzimidazole (0.022 mol) in DMSO (20 mL) and the mixture was stirred for 30 min at 20 °C, and the corresponding **2a**, **2b** or **2c** (0.01 mol; 5.67 g, 6.15 g and 6.60 g, respectively) was added portion-wise under vigorous stirring in a water bath. The stirring was continued for another 2 h, and the water (200 mL) was then added to the mixture which was extracted with chloroform (6 × 25 mL). The combined extracts were washed with water and dried over anhydrous magnesium sulphate. The solvent was evaporated off and the product was recrystallized from methanol.

3.3.4.1 *N,N*-bis[(Benzimidazol-1-yl)ethyl]-4-methylbenzenesulphonamide (3a)

White solid; Yield: 94%; a single crystal was obtained properly for X-ray structural determination by using DMF; m.p.192–194 °C; FTIR (cm^{-1}): 3,098, 3,047 (C-H)$_{Ar}$,

2,927 (C-H)$_{Aliph}$, 1,666, 1,615, 1,598 (C=N)$_{Ar}$, 1,498, 1,460 (C=C)$_{Ar}$, 1,362, 1,150 (O=S=O); ^{1}H-NMR (DMSO-d_6) δ ppm: 8.09 (s, 2H, C-H$_{BImidazole}$), 7.64–7.60 (m, 4 H, 2 × C-H$_{Ar}$, 2 × C-H$_{BImidazole}$), 7.44 (d, 2H, J = 8.15 Hz, C-H$_{Ar}$), 7.30–7.19 (m, 6H, C-H$_{BImidazole}$), 4.27 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.49 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N), 2.33 (s, 3H, -CH$_3$); ^{13}C-NMR (DMSO-d_6) δ ppm: 144.57 (2 × CH$_{BImidazole}$), 144.20 (C$_{Ar}$-S), 143.84 (2 × C$_{BImidazole}$), 135.36 (C$_{Ar}$-CH$_3$), 134.04 (2 × C$_{BImidazole}$), 130.43 (2 × CH$_{Ar}$), 127.49 (2 × CH$_{BImidazole}$), 123.07 (2 × CH$_{BImidazole}$), 122.15 (2 × CH$_{Ar}$), 120.06 (2 × CH$_{BImidazole}$), 110.59 (2 × CH$_{BImidazole}$), 48.71 (2 × CH$_2$-N), 43.77 (2 × CH$_2$-N$_{Ar}$), 21.51 (CH$_3$); EIMS (m/z): 459 (16%, M$^+$), 278 (100%), 304 (10%), 278 (13%), 172 (36%), 155 (24%), 131 (87%), 91 (75%).

3.3.4.2. *N,N*-bis[2-(Benzimidazol-1-yl)ethyl]-4-methoxybenzenesulphonamide (3b)

White solid; Yield: 84%; m.p. 138–140 °C; FTIR (cm^{-1}): 3,096, 3,055 (C-H)$_{Ar}$, 2,910 (C-H)$_{Aliph}$, 1,666, 1,615, 1,597 (C=N)$_{Ar}$, 1,494, 1,460 (C=C)$_{Ar}$, 1,375, 1,164 (O=S=O), 1,220 (C-O-C); ^{1}H-NMR (DMSO-d_6) δ ppm: 8.09 (s, 2H, C-H$_{BImidazole}$), 7.68–7.62 (m, 4H, 2 × C-H$_{Ar}$, 2 × C-H$_{BImidazole}$), 7.45 (d, 2H, J = 8.15 Hz, C-H$_{Ar}$), 7.28–7.15 (m, 4H, C-H$_{BImidazole}$), 7.00–6.96 (m, 2H, C-H$_{BImidazole}$), 4.27 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N), 3.80 (s, 3H, OCH$_3$), 3.48 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N); ^{13}C-NMR (DMSO-d_6) δ ppm: 163.23 (C$_{Ar}$-O), 144.51 (2 × CH$_{BImidazole}$), 143.83 (2 × C$_{BImidazole}$), 134.07 (2 × C$_{BImidazole}$), 129.78 (C$_{Ar}$-S), 129.70 (2 × CH$_{Ar}$), 123.05 (2 × CH$_{BImidazole}$), 122.19 (2 × CH$_{BImidazole}$), 120.08 (2 × CH$_{BImidazole}$), 115.10 (2 × CH$_{Ar}$), 110.60 (2 × CH$_{BImidazole}$), 56.18 (O-CH$_3$), 48.66 (2 × CH$_2$-N), 43.75 (2 × CH$_2$-N); EIMS (m/z): 475 (20%, M$^+$), 344 (100%), 304 (10%), 278 (13%), 172 (44%), 107 (35%), 131(75%), 91(80%).

3.3.4.3. *N,N*-bis[(Benzimidazol-1-yl)ethyl]-4-nitrobenzenesulphonamide (3c)

Pale green solid; Yield: 62%; m.p. 80–82 °C; FTIR (cm^{-1}): 3,102, 3,055 (C-H)$_{Ar}$, 2,950 (C-H)$_{Aliph}$, 1,660, 1,615, 1,598 (C=N)$_{Ar}$, 1,510, 1,485 (C=C)$_{Ar}$, 1,360, 1,178

(O=S=O), 1,529, 1,340 (Ar-NO$_2$); ^{1}H-NMR (DMSO-d_6) δ ppm: 8.16 (s, 2H, C-H$_{BImidazole}$), 7.78–7.73 (m, 4H, 2 × C-H$_{Ar}$, 2 × C-H$_{BImidazole}$), 7.52 (d, 2H, J = 8.15 Hz, 2 × C-H$_{Ar}$), 7.31–7.22 (m, 4H,C-H$_{BImidazole}$), 6.99–6.94 (m, 2H, C-H$_{BImidazole}$), 4.23 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N), 3.54 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N); ^{13}C-NMR (DMSO-d_6) δ ppm: 153.12 (C$_{Ar}$-NO$_2$), 145.57 (2 × CH$_{BImidazole}$), 143.65 (2 × C$_{BImidazole}$), 134.12 (2 × C$_{BImidazole}$), 130.04 (C$_{Ar}$-S), 128.44 (2 × CH$_{Ar}$), 124.95 (2 × CH$_{BImidazole}$), 120.34 (2 × CH$_{BImidazole}$), 118.88 (2 × CH$_{BImidazole}$), 117.10 (2 × CH), 111.07 (2 × CH$_{BImidazole}$), 50.37 (2 × CH$_2$-N), 44.75 (2 × CH$_2$-N); EIMS (m/z): 490 (16%, M$^+$), 359 (100%), 304 (20%), 278 (30%), 186 (45%), 22 (75%).

3.3.4.4. *N,N*-bis[(Imidazol-1-yl)ethyl]-4-methylbenzenesulphonamide (4a)

White solid; Yield: 82%; a single crystal was obtained for X-ray analysis by using acetonitrile; m.p. 92–94 °C; FTIR (cm^{-1}) 3,093 (C-H)$_{Ar}$, 2,975 (C-H)$_{Aliph}$, 1,597 (C=N)$_{Ar}$, 1,510, 1,457 (C=C)$_{Ar}$, 1,351, 1,159 (O=S=O); ^{1}H-NMR (DMSO-d_6) δ ppm: 7.72 (d, J = 8.15 Hz, 2 × C-H$_{Ar}$), 7.54 (s, 2 × C-H$_{Imidazole}$), 7.41(d, J = 8.15 Hz, 2 × C-H$_{Ar}$), 7.12 (s, 2H, C-H$_{Imidazole}$), 6.89 (s, 2H, C-H$_{Imidazole}$), 3.96 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N), 3.32 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N), 2.39 (s, 3H, CH$_3$); ^{13}C-NMR (DMSO-d_6) δ ppm: 144.28 (C$_{Ar}$-S), 137.87 (2 × CH$_{Imidazole}$), 135.53 (C$_{Ar}$-CH$_3$), 130.49 (2 × CH$_{Ar}$), 128.99 (2 × CH$_{Imidazole}$), 127.56 (2 × CH$_{Ar}$), 119.95 (2 × CH$_{Imidazole}$), 50.30 (2 × CH$_2$-N), 45.75 (2 × CH$_2$-N), 21.49 (-CH$_3$); EIMS (m/z): 359 (10%, M$^+$), 278 (100%), 204 (20%), 155 (22%), 122 (39%), 91 (97%).

3.3.4.5. *N, N*-bis[2-(Imidazol-1-yl)ethyl]-4-methoxybenzenesulphonamide (4b)

Off-white solid; Yield: 90%; m.p. 66–68 °C; FTIR (cm^{-1}): 3,100 (C-H)$_{Ar}$, 2,855 (C-H)$_{Aliph}$, 1,584 (C=N)$_{Ar}$, 1,530, 1,460 (C=C)$_{Ar}$, 1,360, 1,170 (O=S=O), 1,238 (C-O-C); ^{1}H-NMR (DMSO-d_6) δ ppm: 7.76 (d, J = 8.61 Hz, 2H, C-H$_{Ar}$), 7.55 (s, 2H, C-H$_{Imidazole}$), 7.14–7.10 (m, 4H, 2 × C-H$_{Ar}$, 2 × C-H$_{Imidazole}$), 6.89 (s, 2H, C-H$_{Imidazole}$), 3.97 (t, J = 6.80

Hz, 4H, 2 × CH$_2$-N), 3.82 (s, 3H, O-CH$_3$), 3.31 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N); ^{13}C-NMR (DMSO-d_6) δ ppm: 163.34 (C$_{Ar}$-O), 137.92 (2 × CH$_{Imidazole}$), 129.95 (2 × CH$_{Imidazole}$), 129.86 (C$_{Ar}$-S), 129.01 (2 × CH$_{Ar}$), 120.06 (2 × CH$_{Imidazole}$), 115.23 (2 × CH$_{Ar}$), 56.24 (O-CH$_3$), 50.24 (2 × CH$_2$-N), 45.67 (2 × CH$_2$-N); EIMS (*m/z*): 375 (22%, M$^+$), 294 (100%), 204 (20%), 171 (36%), 122 (35%), 107 (35%).

3.3.4.6 *N,N*-bis[(Imidazol-1-yl)ethyl]-4-nitrobenzenesulphonamide (4c)

Pale green solid; Yield: 54%; m.p. 46–48 °C; FTIR (cm^{-1}): 3,080 (C-H)$_{Ar}$, 2,890 (C-H)$_{Aliph}$, 1,620 (C=N)$_{Ar}$, 1,574, 1,460 (C=C)$_{Ar}$, 1,375, 1,185 (O=S=O), 1,520, 1,355 (Ar-NO$_2$); ^{1}H-NMR (DMSO-d_6) δ ppm: 7.96 (d, J = 8.60 Hz, 2H, C-H$_{Ar}$), 7.78 (s, 2H, C-H$_{Imidazole}$), 7.36–7.32 (m, 4H, 2 × C-H$_{Ar}$, 2 × C-H$_{Imidazole}$), 6.95 (s, 2H, C-H$_{Imidazole}$), 3.95 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N), 3.55(t, J = 6.80 Hz, 4H, 2 × CH$_2$-N); ^{13}C-NMR (DMSO-d_6) δ ppm: 149.03 (C$_{Ar}$-NO$_2$), 138.23 (2 × CH$_{Imidazole}$), 130.11 (2 × CH$_{Imidazole}$), 129.78 (C$_{Ar}$-S), 128.12 (2 × CH$_{Ar}$), 122.06 (2 × CH$_{Imidazole}$), 112.14 (2 × CH$_{Ar}$), 48.20 (2 × CH$_2$-N), 43.09 (2 × CH$_2$-N); EIMS (*m/z*): 390 (20%, M$^+$), 309 (60%), 204 (20%), 186 (30%), 122 (100%), 81 (75%).

3.3.5 Synthesis 2-Mercaptobenzimidazole (6)

This compound was prepared according to the modified procedure by Wang and Liu (2007). *o*-Phenylenediamine (7 g, 0.065 mol) was dissolved in absolute ethanol (40 mL) in a 250 mL flask. Carbon disulphide (10 mL) was then added to the solution followed by the addition of a solution of potassium hydroxide (4.35 g, 0.077 mol) in water (25 mL). The reaction mixture was thoroughly stirred and refluxed for 5 h. It was initially yellow, then turned to brown as the reaction progressed. Evolution of hydrogen sulphide gas was observed. After completion of the reaction, the mixture was poured into a beaker with ice-water and acidified with 4N hydrochloric acid to pH 4–5 to obtain a white precipitate. The precipitate was then filtered and recrystallized from ethanol.

White solid; Yield 84%; m.p. 303–305 °C; FTIR (cm^{-1}): 3,250 (N-H), 1,557 (C=C)$_{Ar}$, 1,633 (C=O), 1,517 (C=N).

3.3.6 Synthesis 2-((Benzimidazol-2-yl)methylthio)-benzimidazole (8)

This compound was prepared according to modified procedure by S. Satyanarayana (2004). Sodium (0.85 g, 0.037 mol) was added to a solution of 2-mercaptobenzimidazole (5 g, 0.033 mol) in anhydrous methanol (60 mL) and the mixture was vigorously stirred for 20 minutes. 2-Chloromethylbenzimidazole (5.55 g, 0.033 mol) was added portion-wise to the mixture and left to stir for 2 h. A yellow precipitate was formed, filtered and washed with methanol, cold water and dried in an oven. The crude product was recrystallized from tetrahydrofuran to give a white solid of the title compound. White solid; Yield: 96%; m.p. 255–257 °C; FTIR (cm^{-1}): 3,372 (N-H), 3,090 (C-H)$_{Ar}$, 2,975 (C-H)$_{Aliph}$, 1,621 (C=N)$_{Ar}$, 1,590 (C=C)$_{Ar}$, 748 (C-S); ^{1}H-NMR (DMSO-d_6) δ ppm: 12.52 (s, H, N-H), 12.23 (s, H, N-H), 7.41–7.32 (m, 4H, C-H$_{Ar}$), 6.97–6.90 (m, 4H, C-H$_{Ar}$), 4.93 (s, 2H, CH$_2$-S); ^{13}C-NMR (DMSO-d_6) δ ppm: 153.11 (C$_{Ar}$-S), 149.73 (C$_{Ar}$-S-CH$_2$), 140.32, 139.66 (4 × C$_{Ar}$), 125.34, 123.92 (4 × CH$_{Ar}$), 114.53, 116.03 (4 × CH$_{Ar}$) 33.12 (CH$_2$).

3.3.7 Synthesis *N*-4-Methylbenzenesulphonyl((*N*-(4-methylbenzenesulphonyl)benzimidazol-2-yl)methylthio)-benzimidazole (9)

A solution of *p*-toluenesulphonyl chloride (7.44 g, 0.018 mol) in pyridine (25 mL) was added drop-wise to a solution of 2-((benzimidazol-2-yl)methylthio)-benzimidazole (**8**) (5 g, 0.018 mol) in pyridine (25 mL) at 0 °C, within 3 h. The mixture was stirred at room temperature and left overnight. It was then quenched with ice-water, stirred for another 20 minutes, extracted with dichloromethane (5 × 30 mL) and washed with distilled water. The organic layer was dried over anhydrous magnesium sulphate and solvent evaporated off. The crude product was purified by using flash chromatography with hexane-ethyl acetate (4:1, v/v) as eluent. The obtained solid was recrystallized from

acetonitrile to give colourless crystals of compound (**9**). Colourless crystals; Yield 52%; m.p. 204–206 °C; FTIR (cm^{-1}) 3,087 (C-H)$_{Ar}$, 2,990 (C-H)$_{Aliph}$, 1,660, 1,616 (C=N)$_{Ar}$, 1,593, 1,462 (C=C)$_{Ar}$, 1,365, 1,170 (O=S=O), 752 (C-S); ^{1}H-NMR (CDCl$_3$) δ ppm: 7.98–7.89 (m, 6H, C-H$_{Ar}$), 7.64–7.49 (m, 2H, C-H$_{Ar}$), 7.38–7.24 (m, 6H, C-H$_{Ar}$), 7.19 (d, J = 8.61, 2H, C-H$_{Ar}$), 5.18 (s, 2H, CH$_2$), 2.31, 2.37 (two singlets, 6H, 2 × CH$_3$); ^{13}C-NMR (CDCl$_3$) δ ppm: 151.81 (C$_{BImidazole}$-S), 149.43 (C$_{BImidazole}$-CH$_2$-S), 146.42, 146.18 (2 × C$_{Ar}$-S), 143.22, 141.80 (2 × C$_{BImidazole}$-N), 135.04, 134.57 (2 × C$_{Ar}$-CH$_3$), 133.98, 133.16 (2 × C$_{BImidazole}$-N), 130.38, 130.15 (4 × CH$_{Ar}$), 127.54, 127.45 (4 × CH$_{Ar}$), 125.52, 124.91, 124.69, 124.14, 120.56, 118.95, 113.56, 112.95 (8 × CH$_{BImidazole}$), 31.20 (CH$_2$-S), 21.80, 21.77 (2 × CH$_3$); EIMS (*m/z*): 588 (45%, M$^+$), 433 (80%), 278 (35%), 155 (85%), 148 (12%), 91 (100%).

3.3.8 Synthesis 4-Methyl-*N*-(2-{2-[2-(4-methylbenzenesulphonamido)ethoxy]ethoxy}ethyl)benzenesulphonamide (11)

p-Toluenesulphonyl chloride (5.66 g, 0.029 mol) was dissolved in dry dichloromethane (25 mL) and added drop-wise to a stirring solution of 1,8-diamino-3,6-dioxaoctane(2,2′-(ethylenedioxy)bis-(ethyl amine) (2 g, 0.013 mol) and triethylamine (4.42 mL, 0.031 mol) in dichloromethane (25 mL) at 0 °C. The mixture was stirred further at room temperature for overnight and extracted with water and saturated solution of NaHCO$_3$ (3 × 15 mL). The organic layer was dried over anhydrous magnesium sulphate and the solvent was evaporated off. Colourless crystals were obtained through slow evaporation of methanolic solution at room temperature. Yield: 92%; m.p. 88–90 °C; FTIR (cm^{-1}) 3,276 (NH), 3,090 (C-H)$_{Ar}$, 2,921, 2,898, 2,872 (C-H)$_{Aliph}$, 1,596 (C=C)$_{Ar}$, 1,317, 1,152 (O=S=O), 1,088 (C-O-C), 1,124 (C-C-O); ^{1}H-NMR (CDCl$_3$) δ ppm: 7.73 (d, J = 8.61 Hz, 4H, C-H$_{Ar}$), 7.27 (d, J = 8.61 Hz, 4H, C-H$_{Ar}$), 5.50 (t, J = 5.89 Hz, 2H, 2 × NH), 3.50 (t, J = 5.44 Hz, 8H, 4 × CH$_2$O), 3.09 (q, J = 8.15 Hz, 4H, 2 × CH$_2$-NH), 2.39 (s, 6H, 2 × CH$_3$); ^{13}C-NMR (CDCl$_3$) δ ppm: 143.45 (2 × C$_{Ar}$-S), 137.07

$(2 \times C_{Ar}\text{-}CH_3)$, 129.78 $(4 \times CH_{Ar})$, 127.18 $(4 \times CH_{Ar})$, 70.43 $(2 \times CH_2\text{-}O)$, 69.78 $(2 \times CH_2\text{-}O)$, 42.99 $(2 \times CH_2\text{-}N)$, 21.59 $(2 \times CH_3)$; EIMS (m/z): 456 (25%, M$^+$), 301 (100%), 155 (70%), 146 (35%), 91 (90%).

3.3.9 Antibacterial Evaluation

The antibacterial activity of the synthesized compounds **3a–c**, **4a–c**, **9** and **11** was tested against standard strains of ten bacteria. They were obtained from the collection of the School of Biosciences and Biotechnology, Faculty of Science and Technology, University Kebangsaan, Malaysia. These strains included Gram positive bacteria: *Streptococcus pyogenes* ATCC19615, *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC6051, *Rodococcus Ruber* ATCC27863, *Enterococcus faecalis* ATCC 29212, *Staphylococcus epidermidis* ATCC12228 and Gram negative bacteria*: Escherichia coli* ATCC10538, *Salmonella typhimurium* ATCC14028, *Pseudomonas aeruginosa* ATCC15442, *Acinetobacter calcoaceticus* ATCC 23055.

The antibacterial activity was assessed in terms of minimum inhibitory concentrations (MICs) by using microbroth dilution assays and according to the CLSI guidelines (Wikler, 2009). All the tested compounds were dissolved in dimethylsulfoxide (DMSO) which was used as negative control with concentrations range from 0.05 to 0.5 mg/mL. Commercial antibiotics amoxicillin and kanamycin in the same range of concentrations were used as a positive control. The bacterial stock cultures were maintained on nutrient agar plates. A loopful of bacterial cells from the nutrient agar plates was inoculated into 100 mL nutrient broth in 250 mL side arm Erlenmeyer flask and incubated at 37 °C for 16 h with vigorous shaking. After incubation, the culture was diluted with fresh media to give an O.D600 nm of 0.1. Fifty µL of standardized 18 h incubated bacterial culture was introduced into test tubes containing 5 mL media followed by the addition of various concentrations of the compounds studied. The MIC was recorded as the lowest concentration that inhibits the

growth of the bacterial strains. All assays were performed in triplicate and MIC's values are given in mg/mL.

3.4 CONCLUSIONS

Novel imidazole and benzimidazole compounds with a sulphonamido moiety as substituent, *i.e.*, **3a–c**, **4a–c**, and **9** in addition to novel bis-sulphonamide compound *i.e.*, **11** were successfully synthesized through simple methods. The structures for the synthesized compounds were confirmed by FTIR, NMR, and HRMS studies. These compounds were evaluated for *in vitro* antibacterial activities against ten strains of bacteria. Compounds **3c**, **9** and **11** demonstrated the highest bioactivities among the compounds, however, most of them showed significant activities for both Gram-positive and Gram-negative bacteria. Such results are encouraging for synthesis of promising new complexes from these compounds with several metals to evaluate their biological activity in the near future. Further studies of these new synthesized sulphonamide derivatives by the same authors are in progress related to their use as ligands and their complexes.

CHAPTER 4: BIS-IMIDAZOLIUM AND BENZIMIDAZOLIUM BASED GEMINI-TYPE IONIC LIQUIDS STRUCTURE: SYNTHESIS AND ANTIBACTERIAL EVALUATION

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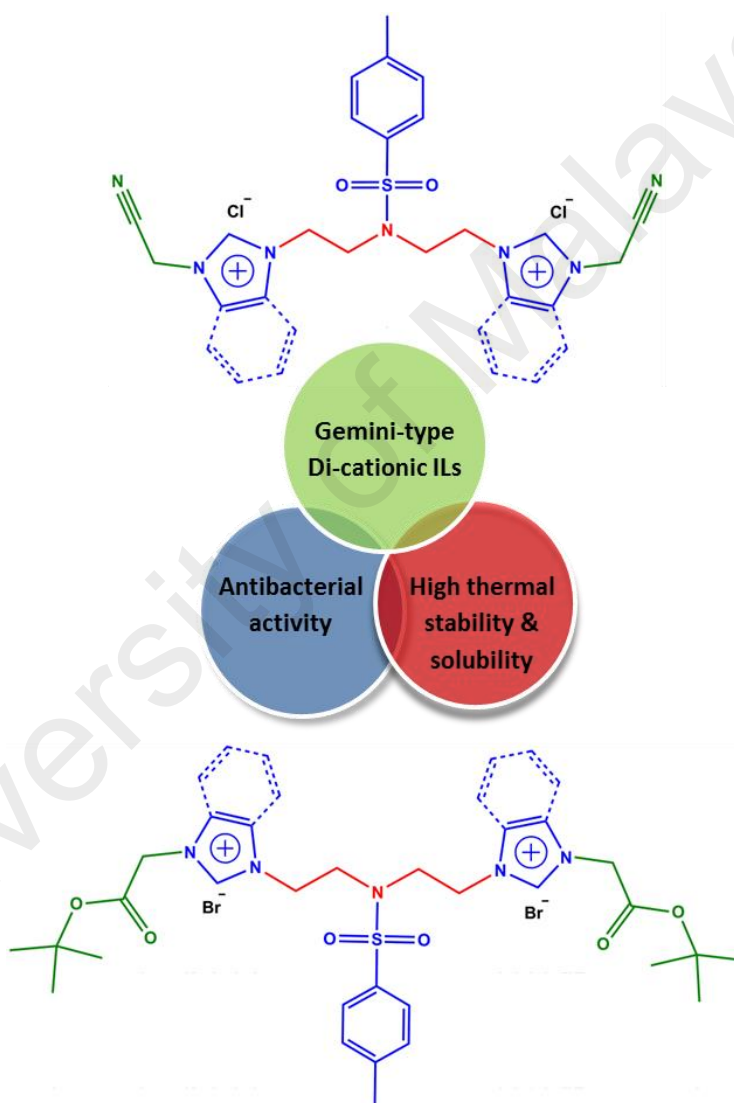
The incorporated benzenesulfonamide moiety and the active side substituents into di-imidazolium and benzimidazolium cations enhanced both antibacterial activity and miscibility for the synthesized gimini type ILs.

4.1 INTRODUCTION

Ionic liquids (ILs) are salts typically consisting of large organic cations containing various substituents (Davis, 2004; Wasserscheid & Welton, 2007) associated with organic or inorganic anions (Robin & Kenneth, 2002; Welton, 1999). They are exhibiting several unique chemical and physical properties, such as extremely low vapour pressure, low melting point, non-flammability, wide electrochemical window, excellent solvation and high thermal stability. Furthermore, through the modification of cation and anion, ILs can be tuned to be miscible with either low polarity organic solvents including: hexanes, toluene, ether, super critical CO_2 or high polarity solvents such as water and ethanol (Handy, 2003). The interest in ILs as 'greener' solvents has dramatically expanded to include a wide unexpected range of applications that have been reported in synthesis and biotechnology.

ILs with molecular structure of Gemini surfactants (Geminal ILs) are a new class of amphiphilic molecules containing two head groups (two identical or dissimilar cationic moieties) and two aliphatic chains, linked by a rigid or flexible spacer. Comparing to traditional ILs, geminal dicationic liquids have shown superior physical properties (Anderson *et al.*, 2005; Ding, Zha, Zhang, & Wang, 2007b; Payagala *et al.*, 2007; Shirota *et al.*, 2011) in: thermal stability, solubility in aqueous media, high density, interface property, lower critical micelle concentration (CMC), and unusual rheological properties. Accordingly, they have multiple promising applications in life science, petro-chemistry, medicine, *etc.* Furthermore, dicationic ILs as multifunctional ions have an exclusive approach to "tune" or alter their physicochemical properties to a greater range than more traditional monocationic ILs. The "tenability" or structural variations include the effect of the cationic part symmetry (*i.e.*, identical or not), the length and type of both spacer and the side chains, as well as the type of counteranions.

Recently, several ammonium-based dicationic phosphate salt liquids have prepared and characterized (Engel & Cohen, 2002; Lall *et al.*, 2002; Lall *et al.*, 2000; Wishart *et al.*, 2005). In the meanwhile, some dicationic ILs based-imidazolium pyridinium and ammonium with polyether linker (Yoshizawa, Ito-Akita, & Ohno, 2000) have been synthesized by Ohno and co-workers (Ito, Nishina, & Ohno, 2000). Additionally, two studies by Anderson *et al.*, (Anderson *et al.*, 2005) and Payagala *et al.*, (Payagala *et al.*, 2007) that deal with synthesis and physicochemical properties manipulation of symmetrical and unsymmetrical geminal dicationic ILs, respectively. They have characterized several properties including thermal stability, surface tension, density, miscibility with a polar and nonpolar solvent, and shear viscosity of imidazolium and pyrrolidium cation based ILs. Thermal stabilities of the symmetrical and unsymmetrical dicationic ILs are higher than their corresponding conventional monocationic ILs. Precisely, Imidazolium and pyridinium geminal dicationic ILs have shown an increased thermal stability, with the onset temperatures of decomposition (T_{onset}) of about 150 °C above the decomposition temperature of the monocationic ILs (Anderson *et al.*, 2005; Payagala *et al.*, 2007). Thermogravimetric analysis (TGA) at elevated temperatures is used to evaluate thermal stability of many dicationic ILs. This method of short-term stability, called ramped temperature analysis method with most common heating rates: 10 °C min^1 and 20 °C min^{-1}.(Awad *et al.*, 2004; Valkenburg, Vaughn, Williams, & Wilkes, 2005) Multiple factors including the great charge and intermolecular interactions, density, molecular weight and shear viscosity associated with small free volume, were used to attribute the observed high thermal stability of dicationic ILs (Huang, Han, Zhang, & Armstrong, 2007; Maton, De Vos, & Stevens, 2013).

From the ILs' structure point of view, Poly-functionalized heterocyclic compounds containing imidazole and its derivatives are acquiring more importance due to their biological activity. Most ILs contain heterocyclic derivatives as cations, *e.g.*

imidazolium, benzimidazolium, pyridinium, pyrrolium, pyrrolidinium and ILs with bridged structures. Drug designs based on high therapeutic properties of the imidazole and benzimidazole are considered as an advantage towards synthesize number of novel clinical agents against various types of diseases. Moreover, extensive biochemical and pharmacological studies have confirmed imidazole and benzimidazole as effective compounds in treating various strains of microorganisms (Demberelnyamba *et al.*, 2004; Docherty & Kulpa, 2005; Günal, Kaloğlu, Özdemir, Demir, & Özdemir, 2012; Mester *et al.*, 2015; Pernak *et al.*, 2001). Their antibacterial and antifungal effects are attributed to cationic interactions with negatively charged parts of bacterial membranes (Papo & Shai, 2003). Furthermore, benzenesulphonamide moiety is well known for its several pharmacological activities, individually or when incorporated with other bioactive moieties within the same molecule (Alyar, Zengin, Özbek, & Karacan, 2011; Basanagouda *et al.*, 2010; Krátký *et al.*, 2012). Typically, sulphonamide compounds are widely studied due to their chemotherapeutic and the interesting properties related antibacterial (Aslan, Özcan, & Karacan, 2012; Weidner-Wells & Macielag, 2000), anti-inflammatory (Bano *et al.*, 2011; Rathish *et al.*, 2009), analgesic agents (Carta *et al.*, 2015), antifungal (Ezabadi *et al.*, 2008; Zoumpoulakis *et al.*, 2012) and antiviral (Chen *et al.*, 2010; Kumar, Ramasamy*, et al.*, 2014). Molecular Modeling and Quantitive Structure-activity Relationship (QSAR) method (Aslan *et al.*, 2012; Blatova, Asiri, Al-amshany, Arshad, & Blatov, 2014; Kumar, Narasimhan*, et al.*, 2014; Nieto, Alovero, Manzo, & Mazzieri, 2005), have been used to confirm their antibacterial activity for many applications in the bio-inorganic and metal-based drug chemistry (Alaghaz, Zayed, Alharbi, Ammar, & Elhenawy, 2015; Chohan, Shad, Youssoufi, & Ben Hadda, 2010; Mondelli *et al.*, 2008; Özdemir, Güvenç, Şahin, & Hamurcu, 2009). The enhancement of antibacterial activity of di-imidazole and di-benzimidazole compounds incorporated to sulphonamide moiety has been reported by authors of the previous work

(Al-Mohammed *et al.*, 2013). However, many research works dealt with geminal di-cationic ILs synthesis when it comes to their design (Anderson *et al.*, 2005; Cecchini *et al.*, 2014; Chang *et al.*, 2010; Ding *et al.*, 2007a; Huang *et al.*, 2007; Jadhav & Kim, 2012; Li, Yu, Chen, Li, & Li, 2012; Payagala *et al.*, 2007; Pitawala *et al.*, 2009; Shirota *et al.*, 2011), while limited studies have considered dicationic ILs with a high rigid spacer (Rajakumar, Raja, Selvam, Rengasamy, & Nagaraj, 2009; Rajakumar, Selvam, & Dhanasekaran, 2005). The current work concentrates on synthesis of novel geminal bis-imidazolium and benzimidazolium ILs consist of two substituents symmetric head groups (two identical cations), linked by high rigidity spacer containing benzenesulphonamide moiety in high yield and purity. To explore the structure–activity relationship (SAR) of this novel dicationic IL series that contain multi bioactive moieties, an *in vitro* antibacterial evaluation of halogen ILs against standard strains of six Gram positive and four Gram negative, are investigated. Further, the thermal stability and miscibility of the prepared ILs are indicated as well. The presence of incorporated benzenesulphonamide moiety as well as the active side substituents into di-imidazolium and benzimidazolium cations enhanced both antibacterial activity and miscibility for the synthesized ILs. The effects of anions on antibacterial activity and thermal stability are beyond the scope of this study.

4.2 RESULTS AND DISCUSSION

4.2.1 Synthesis

Compounds *N,N*-bis[(imidazol-1-yl)ethyl]-4-methylbenzenesulphonamide (**3**) and *N,N*-bis [(benzimidazol-1-yl)ethyl]-4-methylbenzenesulphonamide (**4**) were previously synthesized in sufficient purity (Al-Mohammed *et al.*, 2013) and currently used as precursors to produce bis-imidazolium and bis-benzimidazolium dicationic ILs, respectively, Figure 4.1. The highly reactive halides; allyl bromide, propargyl bromide, chloroacetonitrile, 2-bromoethanol, ethyl bromoacetate and *tert*-butyl bromoacetate

were considered for the alkylation reactions, thus, the high yields were not surprising due to easy substitution reaction with both imidazole and benzimidazole rings, Table 4.1.

In current work, all the synthesized halogen (chloride or bromide) ILs are semi-solid to syrup or viscous liquid at room temperature which have been considered as criteria to determine their classification as ILs (Forsyth, Pringle, & MacFarlane, 2004; Seddon, 2003). Generally, ILs tend to be liquid at room temperature, which is attributed to the high conformational degrees of freedom. Moreover, the NTf_2 counter ion confers lower viscosity and decreased melting point compared with halogen precursors. Metathesis of halogen anion to NTf_2^- produced clear liquids at room temperature and clean samples were isolated after a simple workup. The process of counter-ions exchange involved stirring an aqueous solution of halogen ILs with $LiNTf_2$ for a few hours. A good yield of the hydrophobic ILs phase was then separated by extraction with ethyl acetate to produce the pure and clear liquid samples of ILs after organic layer evaporation under reduced pressure. The purity of the NTf_2-ILs was confirmed by ^{13}C and ^{9}F-NMR. Table 4.1 summarizes the synthetic details of the prepared ILs.
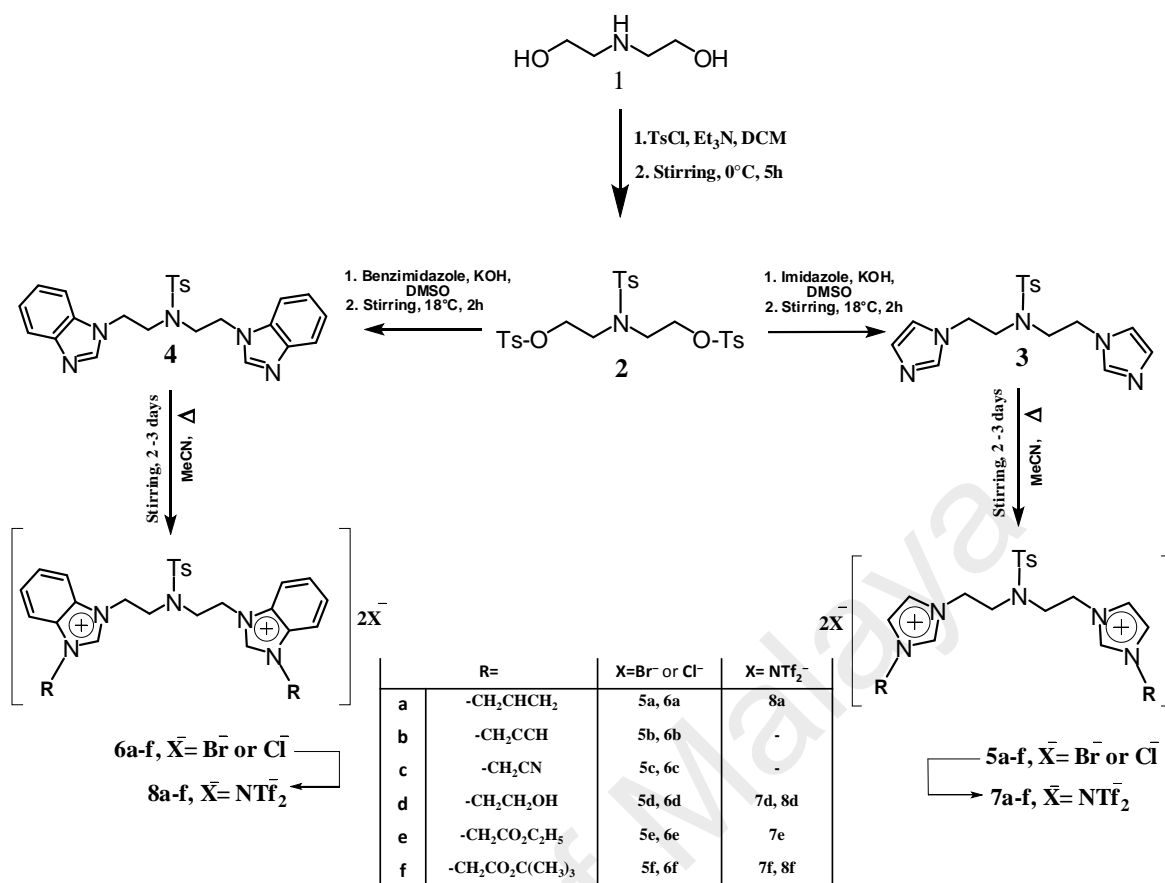
Figure 4.1: Synthesis of imidazolium and benzimidazolium geminal dicationic ILs

	R=	X=Br⁻ or Cl⁻	X= NTf₂⁻
a	-CH₂CHCH₂	5a, 6a	8a
b	-CH₂CCH	5b, 6b	-
c	-CH₂CN	5c, 6c	-
d	-CH₂CH₂OH	5d, 6d	7d, 8d
e	-CH₂CO₂C₂H₅	5e, 6e	7e
f	-CH₂CO₂C(CH₃)₃	5f, 6f	7f, 8f

Table 4.1: Structural and synthetic details of imidazolium and benzimidazolium based dicationic ILs

IL	Cations	Incorporated side groups	Counter ions	Status[c]	M.wt.	Yield (%)
5a	Im[a]	-CH₂CHCH₂	Br⁻	Syrup	601.40	95
5b	Im[a]	-CH₂CCH	Br⁻	Syrup	597.37	98
5c	Im[a]	-CH₂CN	Cl⁻	Liquid	510.44	98
5d	Im[a]	-CH₂CH₂OH	Br⁻	Liquid	609.37	99
5e	Im[a]	-CH₂CO₂C₂H₅	Br⁻	Semi-solid	693.45	96
5f	Im[a]	-CH₂CO₂C(CH₃)₃	Br⁻	Semi-solid	749.55	95
6a	BIm[b]	-CH₂CHCH₂	Br⁻	Liquid	701.51	95
6b	BIm[b]	-CH₂CCH	Br⁻	Syrup	697.48	98
6c	BIm[b]	-CH₂CN	Cl⁻	Syrup	610.56	94
6d	BIm[b]	-CH₂CH₂OH	Br⁻	Liquid	709.49	98
6e	BIm[b]	-CH₂CO₂C₂H₅	Br⁻	Syrup	793.57	98
6f	BIm[b]	-CH₂CO₂C(CH₃)₃	Br⁻	Syrup	849.67	98
7d	Im[a]	-CH₂CH₂OH	NTf₂⁻	liquid	1009.35	83
7e	Im[a]	-CH₂CO₂C₂H₅	NTf₂⁻	liquid	1093.93	96
7f	Im[a]	-CH₂CO₂C(CH₃)₃	NTf₂⁻	liquid	1150.03	95
8a	BIm[b]	-CH₂CHCH₂	NTf₂⁻	liquid	1101.99	90
8d	BIm[b]	-CH₂CH₂OH	NTf₂⁻	liquid	1109.98	87
8f	BIm[b]	-CH₂CO₂C(CH₃)₃	NTf₂⁻	liquid	1250.16	97

[a] Imidazolium, [b] Benzimidazolium, [c] at room temperature

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The spectral data (IR, ^{1}H, ^{13}C, ^{19}F-NMR and mass) are in good agreement with current proposed structures of the newly synthesized ILs. FT-IR spectra for all synthesized ILs (*i.e.* **5a–f**, **6a–f**, **7d-f** and **8a-f**) showed absorption bands at 1,329–1,364 cm^{-1} and 1,151–1,156 cm^{-1} which were assigned to the O=S=O group. These bis-imidazolium and benzimidazolium ILs showed stretching absorption bands at 3,142–3,027 cm^{-1}, 2,990–2,850 cm^{-1}, 1,644–1,590 cm^{-1}, and 1,566–1,443 cm^{-1} attributed to (C-H)$_{Aromatic}$, (C-H)$_{Aliphatic}$, (C=N), and (C=C)$_{Aromatic}$, respectively. The bands at 2,125 cm^{-1} and 2,121 cm^{-1} for compounds **5b** and **6b** were assigned to (C≡C) in propargyl substitutions, while **5c** and **6c** ILs showed characteristic stretching absorption bands at 2,238 cm^{-1} and 2,235 cm^{-1}, respectively, which were assigned to (C≡N). Incorporating ethanol groups into **5d**, **6d**, **7d**, and **8d** ILs showed (O-H) bands at 3,312–3,280cm^{-1}. The IR spectra of compounds **5e-f**, **6e-f** **7e-f** and **8f** showed sharp absorption bands at 1,739–1,748 cm^{-1} which were attributed to carbonyl stretching frequency corresponding to the ester groups. In the ^{1}H-NMR spectra, α-CH$_2$ protons appeared as singlet (compounds **5c**, **5e**, **5f**, **6c**, **6e**, **6f**, **7e**, **7f** and **8f**), doublet (**5a**, **5b**, **6a**, **6b**, **8d**) and triplet (**5d**, **6d**, **7d** and **8d**) at δ 5.16–6.13 ppm, δ 4.88–5.58 ppm, and δ 4.19–4.57, respectively. Moreover, singlet peaks appeared in the range of δ 9.72–10.31 ppm corresponding to isolated C-H of benzimidazolium rings, while these protons showed broad triplet ~ singlet peaks in all imidazolium ILs. The chemical shifts of the imidazole and benzimidazole protons rings' in both imidazolium and benzimidazolium ILs are consistently downfield in comparison to the analogous chemical shifts of the core di-imidazole and di-benzimidazole compounds (Al-Mohammed *et al.*, 2013). These observations are in accord with the presence of positive charges in both ILs kinds, where the higher shifts were recorded with acetonitrile as an active side groups; compounds **5c** and **6c**. The allylic-CH in compounds **5a**, **6a** and **8a** showed characteristic multiplet peaks in the range of δ 5.98–6.15 ppm, while the allylic-CH$_2$

showed four individual doublet peaks with different J constant; 0.98, 1.22, 1.36 Hz, respectively. Further, compounds **5b** and **6b** presented triplet peaks at δ 3.88 and 3.91 ppm, which attributed to propargyl-CH with J constant values of 2.72 and 2.27, respectively. The peak of O-H protons for compounds **5d, 6d, 7d** and **8d** appeared as broad singlet at δ 5.15–5.22 ppm integrating for two protons. In general, imidazolium ILs showed up-field resonance when compared to benzimidazolium ILs with both halogen and NFf$_2$ anions.

^{13}C-NMR was used to assign the carbon skeleton of the synthesized geminal dicationic imidazolium and benzimidazolium ILs. PENDANT experiment (Polarization enhancement nurtured during attached nucleus testing) was applied to differentiate between the methylene (CH$_2$) and methine (CH) carbon signals based on different H-content of carbon atoms that have environments similarity (Homer & Perry, 1995). In PENDANT spectra methyl (CH$_3$) and methine (CH) carbons appeared as positive signals, while methylene (CH$_2$) and quaternary carbon (C) showed negative signals. Figure 4.2 demonstrated ^{13}C-NMR PENDANT spectrum of IL **6a**.

In the ^{13}C-NMR spectra of **5a**, **6a**, and **8a** ILs, the signals around δ 130 ppm and 120 ppm were assigned to allylic CH and CH$_2$, respectively, while the propargyl active side groups in both **5b** and **6b** ILs showed characteristic peaks in the δ 79 ppm for -C- and δ 75 ppm for CH. Additional signals were observed at 114 ppm and 113 ppm, which were assigned to the carbon atom of (CN) for compounds **5c** and **6c**, respectively. The peaks recorded at δ 165−167 ppm were attributed to carbon atom of carbonyl groups in compounds **5e**, **5f**, **6e**, **6f**, **7e**, **7f** and **8f**. Ethanolic carbon atoms in **5d**, **6d**, **7d** and **8d** ILs were determined at 59 ppm. Carbon atoms C-F in **7d–f**, **8a, 8d and 8f** ILs showed quartet peaks with 320 Hz constant J values within the range of 126-114 ppm. The characteristic chemical shifts for F/CF$_3$ were also detected in the ^{19}F-NMR spectra at −80 ppm. With the high resolution mass spectra the identity of the bis-imidazolium

and benzimidazolium ILs was confirmed as a $[M^{+2}-H]-2X^-$; (M= cation and X= anion) in both kinds of IL anions.
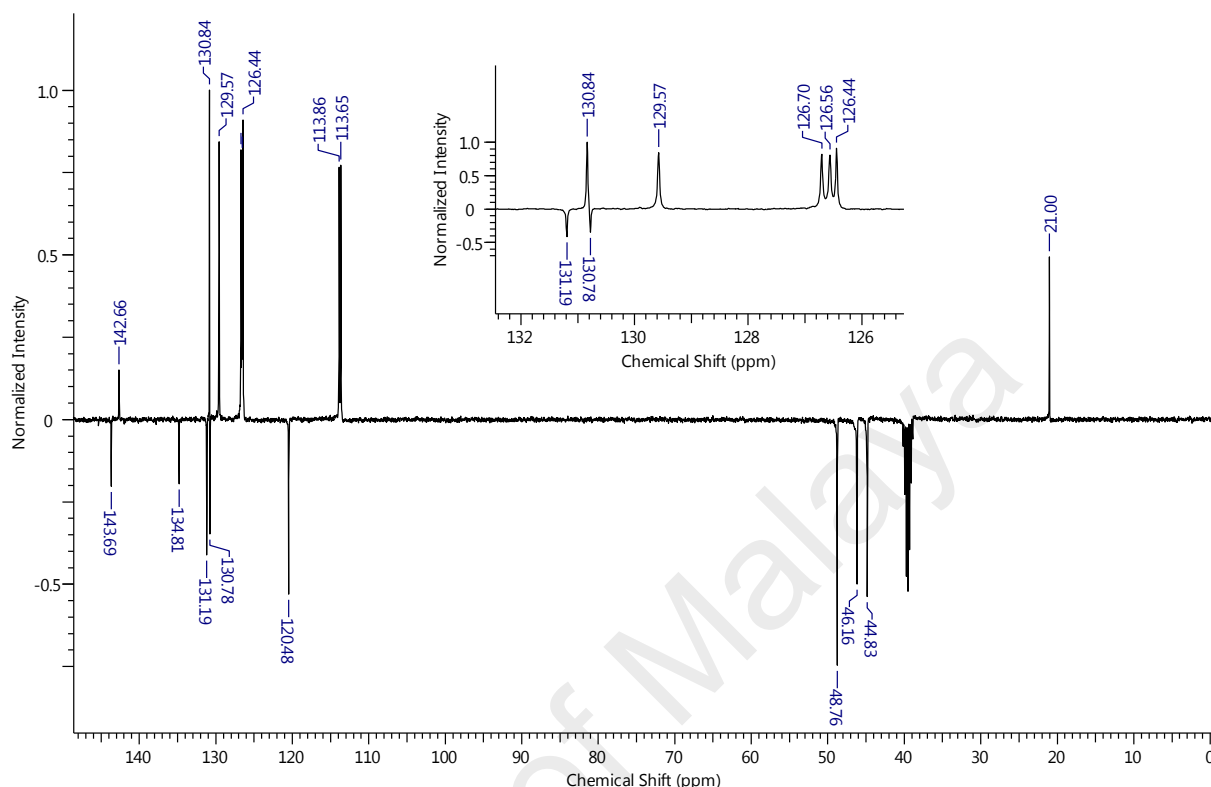
Figure 4.2: ^{13}C-NMR PENDANT of IL **6a**.

4.2.2 Solubility

Solubility behaviour of all synthesized geminal dicationic ILs in water and common organic solvents was evaluated at room temperature. These solvents have a wide range of polarity from highly polar; water or alcohols, gradually to weakly or non-polar solvents like toluene or hexane, respectively. The observations obtained from solubility tests are summarized in Table 4.2.

The IL was considered miscible (if a drop of the IL dissolves in a few drops (1−5) of the solvent), partially miscible (if it dissolves in more than 10 drops of the solvent), or immiscible (if it did not dissolve in 2 ml of the solvent) (Saadeh, Yasseen, Sharif, & Abu Shawish, 2009) and is represented by (+), (±) and (−), respectively. It can be observed that all halogen bis-imidazolium and benzimidazolium ILs are miscible with water while reverse miscibility was noticed for the ILs incorporated to NTf$_2^-$ anion. All

ILs studied for both kinds of anions are totally miscible with acetone, ethyl acetate, tetrahydrofuran and chloroform, while they are shown to be immiscible with hexane. Generally, the introduction of hydroxyl in the side active groups considerably modified the solubility behaviour of ILs **7d** and **8d** with ethanol (Branco, Rosa, Moura Ramos, & Afonso, 2002), while no significant influence has been observed for the rest of ILs when other functional groups changed neither in the introduction benzene ring into imidazolium ILs.

Table 4.2: Solubility of synthesized imidazolium and benzimidazolium based geminal dicationic ILs in various solvents

IL	Water	Ethanol	Acetone	Ethyl acetate	tetrahydrofuran	Chloroform	Toluene	Hexane
5a	+	+	+	+	+	+	+	−
5b	+	+	+	+	+	+	+	−
5c	+	+	+	+	+	+	±	−
5d	+	+	+	+	+	+	±	−
5e	+	+	+	+	+	+	+	−
5f	+	+	+	+	+	+	+	−
6a	+	+	+	+	+	+	+	−
6b	+	+	+	+	+	+	+	−
6c	+	+	+	+	+	+	+	−
6d	+	+	+	+	+	+	+	−
6e	+	+	+	+	+	+	+	−
6f	+	+	+	+	+	+	+	−
7d	−	±	+	+	+	+	±	−
7e	−	−	+	+	+	+	+	−
7f	−	−	+	+	+	+	+	−
8a	−	−	+	+	+	+	+	−
8d	−	±	+	+	+	+	+	−
8f	−	−	+	+	+	+	+	−

(+) miscible - a drop of the compound dissolves in a few drops (1–5) solvent
(±) moderately miscible - dissolves in more than 10 drops solvent
(−) immiscible - did not dissolve in 1-2 ml solvent

The solubility behaviour of the geminal dicationic ILs in water and all common organic solvents was significantly similar to mono-cationic ILs (Freire *et al.*, 2010; Freire, Santos, Fernandes, Coutinho, & Marrucho, 2007; He, Wang, Yao, Song, & Yao,

2014), whereas the halogen and NTf_2^- dicationic ILs were noticed to be miscible and immiscible with water, respectively. Obviously, the presence of hydrophobic anion (NTf_2^-) exceeds the coordinating nature of the bromide (or chloride) anion to produce immiscible ILs with water. Thus, the individual cations and anions can be tuneable to produce ILs with the desired properties and characteristics.

4.2.3 Antibacterial Activities

Microbroth dilution bioassay was used to evaluate the antibacterial activities of the synthesized halogen imidazolium and benzimidazolium geminal dicationic ILs against representative standard strains of Gram-positive and Gram-negative bacteria. Minimum inhibitory concentrations MIC (mg/mL) of the studied dicationic ILs were determined, and the results are listed in Table 4.3. The majority of these ILs showed significant antibacterial activity towards most of the selected microorganisms as shown in Figure 4.3. According to the studies of structure-activity relationship (SAR), the incorporation of two different pharmacophores within the same molecule would enhance the resulting compounds' biological activities (Chen *et al.*, 2010; Jallapally, Addla, Yogeeswari, Sriram, & Kantevari, 2014; Plech *et al.*, 2011). Therefore, the presence of incorporated benzenesulphonamide moiety adjacent to the imidazolium and benzimidazolium core ILs, successfully promoted the antibacterial activity of the produced geminal dicationic ILs. Based on antimicrobial activity studies of imidazolium ILs, the halogen anions showed the least toxicity (Docherty & Kulpa, 2005; Lee, Chang, Choi, & Koo, 2005; Matzke *et al.*, 2007; Pernak, Goc*, et al.*, 2004; Pernak, Sobaszkiewicz, & Mirska, 2003), while ILs bioactivity is largely driven by hydrophobicity and active side substitutions (or alkyl chain branching) of the cations (Al-Mohammed, Duali Hussen, Ali, Alias, & Abdullah, 2015; Al-Mohammed, Duali Hussen, Alias, & Abdullah, 2015; Bernot, Brueseke, Evans-White, & Lamberti, 2005; Garcia-Lorenzo *et al.*, 2008; Ranke *et al.*, 2004). Due to the similarity of ILs structure to detergents, pesticides and antibiotics, the

proposed mechanism of ILs toxicity is through membrane disruption where the toxic effect may be related to a common cellular structure or process (Docherty & Kulpa, 2005; Pernak & Chwała, 2003). Further, ILs as a cationic surfactant may cause disruption in membrane-bound protein due to their interfacial properties, and the induced polar narcosis effect (Bernot, Kennedy, *et al.*, 2005). The current ILs substance attacked the lipid structure of membrane (lipo-polysaccharide layer) where the sulphonyl group of sulphonamide moiety interfered with cell metabolism. Thus, comparing to the previously prepared core compounds (Al-Mohammed *et al.*, 2013) (**3** and **4**), the cationic substitutions of the geminal dicationic ILs, have successfully enhanced the biological activities of both imidazolium and benzimidazolium ILs. Furthermore, imidazolium ILs showed the highest activities which could be attributed to their higher solubility in water (Table 4.2). The highest antibacterial toxicity was found for ILs with acetonitrile substituent (**5c** and **6c**), while the ILs of *tert*-butyl-ester (**5f** and **6f**) did not display dramatic acute biological activities at the selected concentration range. Against β-lactam resistant Gram-negative bacterium (*Pseudomonas aeruginosa*), all IL compounds except **5b**, showed significant activities in MIC ranging values of 0.1 –0.5 mg/mL when compared to the antibiotic amoxicillin. Moreover, **5c** and **6c** ILs showed considerable antibacterial activities of 0.05 mg/mL MIC value against *Bacillus subtilis*, which required a high dose of amoxicillin (Daniel *et al.*, 2012) (0.25 mg/mL). The antibacterial results of the most tested geminal dicationic ILs demonstrated interesting inhibitory values against *Staphylococcus epidermidis*. The range of MIC values for tested compounds were between 0.05 and 0.5 mg/mL, for **6c** and **5e** sequentially, while β-lactam antibiotic amoxicillin displayed no activity against this strain of Gram-positive bacteria. Against *Acinetobacter calcoaceticus* Gram-negative bacteria, IL **5c** exhibited a significant antibacterial inhibitory effect at 0.05 mg/mL, while both commercial antibiotics amoxicillin and kanamycin exhibited MIC values of 0.15 mg/mL and >0.5

mg/mL, respectively. Moreover, *Enterococcus faecalis*, showed no effect by antibiotic kanamycin at the concentration range of the current study (0.05–0.5 mg/mL), while the dicationic IL compounds **5d**, **5e**, and **6e** demonstrated an inhibitory effect with values of 0.25, 0.25 and 0.3 mg/mL, respectively against this Gram-positive bacterium. Based on bioactive compound results, different compounds reacted variously against bacteria. For these dicationic ILs, strains of Gram-positive bacteria seem to be more sensitive than Gram negative micro-organisms.

Table 4.3: Antibacterial activities of synthesized halogen bis-imidazolium and benzimidazolium ILs.
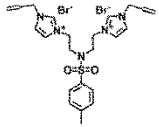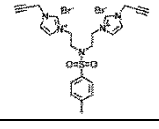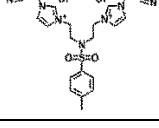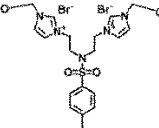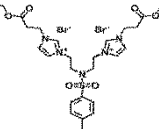
No.	Structure of samples	Bacteria/MICs (mg/mL)									
		Gram-negative bacteria				*Gram-positive bacteria*					
		Escherichia coli	*Salmonella typhimurium*	*Pseudomonas aeruginosa*	*Acinetobacter calcoaceticus*	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Bacillus subtilis*	*Rodococcus ruber*	*Enterococcus faecalis*	*Staphylococcus epidermidis*
5a		0.25	0.40	0.30	0.30	0.10	0.25	0.35	0.40	>0.50	0.30
5b		0.50	>0.50	>0.50	0.50	0.30	0.35	>0.50	0.40	>0.50	>0.50
5c		0.05	0.05	0.10	0.05	0.30	0.10	0.05	0.05	0.10	0.15
5d		0.15	0.20	0.15	0.25	0.25	0.20	0.25	0.15	0.25	0.20
5e		0.40	0.35	0.30	0.30	>0.50	0.50	0.35	0.20	0.25	0.50

Table 4.3: *Cont.*
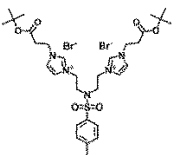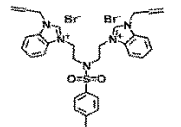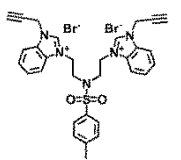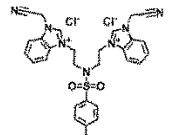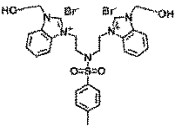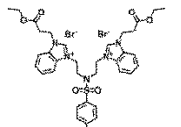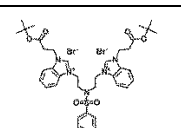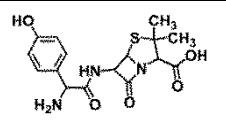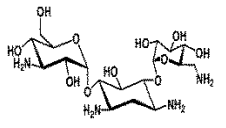
No.	Structure of samples	Bacteria/MICs (mg/mL)									
		Gram-negative bacteria				*Gram-positive bacteria*					
		Escherichia coli	*Salmonella typhimurium*	*Pseudomonas aeruginosa*	*Acinetobacter calcoaceticus*	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Bacillus subtilis*	*Rodococcus ruber*	*Enterococcus faecalis*	*Staphylococcus epidermidis*
5f		0.50	0.40	0.30	0.40	>0.50	>0.50	0.50	>0.5	>0.5	>0.5
6a		0.40	>0.50	0.50	0.45	0.40	0.35	0.40	>0.50	>0.50	0.40
6b		>0.50	>0.50	0.50	>0.50	0.45	0.50	>0.50	>0.50	>0.50	>0.50
6c		0.25	0.05	0.25	0.30	0.10	0.15	0.05	0.20	0.15	0.05

Table 4.3: *Cont.*

No.	Structure of samples	Bacteria/MICs (mg/mL)									
		Gram-negative bacteria				*Gram-positive bacteria*					
		Escherichia coli	*Salmonella typhimurium*	*Pseudomonas aeruginosa*	*Acinetobacter calcoaceticus*	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Bacillus subtilis*	*Rodococcus ruber*	*Enterococcus faecalis*	*Staphylococcus epidermidis*
6d		0.35	0.20	0.40	0.35	0.40	0.40	0.30	0.30	>0.50	0.40
6e		0.30	0.35	0.45	0.30	0.40	0.40	0.35	0.40	0.30	0.30
6f		>0.5	>0.5	0.4	>0.5	0.5	>0.5	>0.5	>0.5	>0.5	>0.5
AM		<0.05	<0.05	nd	0.15	0.05	<0.05	0.25	<0.05	<0.05	nd
KA		<0.05	<0.05	<0.05	>0.5	<0.05	<0.05	<0.05	<0.05	>0.5	<0.05

MIC: Minimum inhibitory concentration, AM: Amoxicillin, KA: Kanamycin, nd: not detected.

Figure 4.3: MIC's Histogram for synthesized ILs (0.05–0.50 mg/mL concentration) versus ten strains of bacteria

4.2.4 Thermal stability

Ramped temperature TGA method (Awad *et al.*, 2004; Huddleston *et al.*, 2001; Valkenburg *et al.*, 2005) (at heating rate of 10 °C min^{-1}), was used to measure the decomposition temperatures of the synthesized halogen imidazolium and benzimidazolium geminal dicationic ILs (*i.e.* **5a-f** and **6a-f**). Ramped temperature experiment (also called step-tangent or dynamic analysis) (Anderson *et al.*, 2005; Baranyai, Deacon, MacFarlane, Pringle, & Scott, 2004) gives rise to a point of thermal degradation, which is termed T_{onset} onset points of decomposition and defined as the value of the intercept of two linear functions: the baseline of zero weight loss and the tangent of weight *vs*. temperature upon decomposition and calculated using the thermal analysis software (Fredlake, Crosthwaite, Hert, Aki, & Brennecke, 2004). The actual degradation already starts at a lower temperature (T_{start}) than the T_{onset} (Crosthwaite, Muldoon, Dixon, Anderson, & Brennecke, 2005). Typically, the ramped temperature

method is also characterized by a temperature of maximum degradation (T_{peak}) in between 10 to 100 ^{o}C higher than T_{onset} (Awad *et al.*, 2004). Moreover $T_{10\%}$ or $T_{50\%}$, which reveals the temperature at a weight loss of 10% and 50%, respectively, were reported and several research works have followed similar technique (Noack *et al.*, 2010; Tao, Tamas, Xue, Simon, & Quitevis, 2014). The decomposition temperatures ($T_{10\%}$), ($T_{50\%}$), (T_{start}), (T_{onset}) as well as the differential peak temperature (T_{peak}), for all samples were listed in Table 4.4.

All the synthesized ILs exhibited good thermal stability with high decomposition temperatures. Generally, ILs bearing imidazolium cations exhibited higher thermal stability compared to those with benzimidazolium, Figures 4.4 and 4.5 demonstrate their thermogravimetric analysis traces, respectively. Further, the ILs containing the cyanide or ethanolic functional side groups (*i.e.* **5c** and **5d**) are the most stable with the highest onset decomposition temperature of 294 and 289 °C, respectively. These di-cationic ILs decompose similarly at the first stage (203–270 ^{o}C for imidazolium and 200–255 ^{o}C for benzimidazolium ILs); subsequently, they have parallel ramps in the decomposition traces, perhaps indicating a similar decomposition mechanism and products.

Generally, imidazolium and benzimidazolium geminal dicationic ILs incorpora- ting to unsaturated side groups showed lower thermal stability than their fully saturated analogues (Anderson *et al.*, 2005). Due to the increasing distance between alkene and nitrogen of the imidazolium ring in **5a** and **6a** ILs, an increase in their thermal stability has been noticed, while the rigidity of alkyne functional groups in **5b** and **6b** ILs gave rise to a decrease in the stability (propargyl *vs.* allyl) (Ferreira, Simões, & Ferreira, 2012).

TGA thermograms of both types of IL reveal three main weight loss regions. The first region at a temperature range of 50 to 200 ^{o}C is due to the evaporation of physically weak and chemically strong bound water. The weight loss of the ILs in this

range is about 5–8 wt. % reflecting an acceptable limit of water content. The second transition region at around 210–500 °C is due to the structural degradation of the ILs with 50–70% total weight loss within these ranges of the decomposition temperatures. The third stage weight loss occurred above 500 °C, probably due to the cleavage backbone of the ILs where the total weight loss in this stage was ~20 % at 900 °C. The decomposition of all tested ILs was almost completed at around 900°C and no further weight loss observed after that. Compared to many traditional mono- and symmetric dicationic imidazolium-based ILs (Anderson *et al.*, 2005; Payagala *et al.*, 2007; Shirota *et al.*, 2011), the prepared geminal dicationic ILs showed a significant high thermal stability, *e.g.*, thermal stabilities ranging from 145, 185, 257 to 300 °C were recorded to (1-butyl-3-methylimidazolium chloride), (1-butyl-3-methylimidazolium bis-(trifluoro-methylsulphonly)imide), (1,5-bis-(3-(2-ethanolyl)-imidazol-1-iumyl)pentane bis(triflu-oromethylsulphonyl)imide), and (1,5-bis-(3-methylimidazol-1-iumyl)pentane nitrate), respectively. The thermal stability results of current synthesized ILs support the high decomposition temperatures feature for imidazolium-based dicationic ILs.

Table 4.4: Thermal decomposition temperatures of the synthesized bis-imidazolium and benzimidazolium ILs

IL	Incorporated side groups	Temperature (°C) corresponding to				
		T_{start}[a]	T_{10}[b]	T_{50}[c]	T_{peak}[d]	T_{onset}[e]
5a	-CH$_2$CHCH$_2$	270	297	299	324	285
5b	-CH$_2$CCH	260	288	310	326	285
5c	-CH$_2$CN	265	285	300	322	294
5d	-CH$_2$CH$_2$OH	248	262	337	330	289
5e	-CH$_2$CO$_2$C$_2$H$_5$	203	235	307	333	233
5f	CH$_2$CO$_2$C(CH$_3$)$_3$	229	279	300	347	274
6a	-CH$_2$CHCH$_2$	250	277	303	338	274
6b	-CH$_2$CCH	265	287	295	324	286
6c	-CH$_2$CN	213	250	265	333	252
6d	-CH$_2$CH$_2$OH	255	282	300	322	281
6e	-CH$_2$CO$_2$C$_2$H$_5$	200	232	307	331	223
6f	CH$_2$CO$_2$C(CH$_3$)$_3$	208	247	292	326	238

Decomposition temperatures, (°C), corresponding to: [a] the started decomposition, [b] at 10 % weight loss, [c] at 50 % weight loss, [d] differential peak, [e] the onset decomposition.
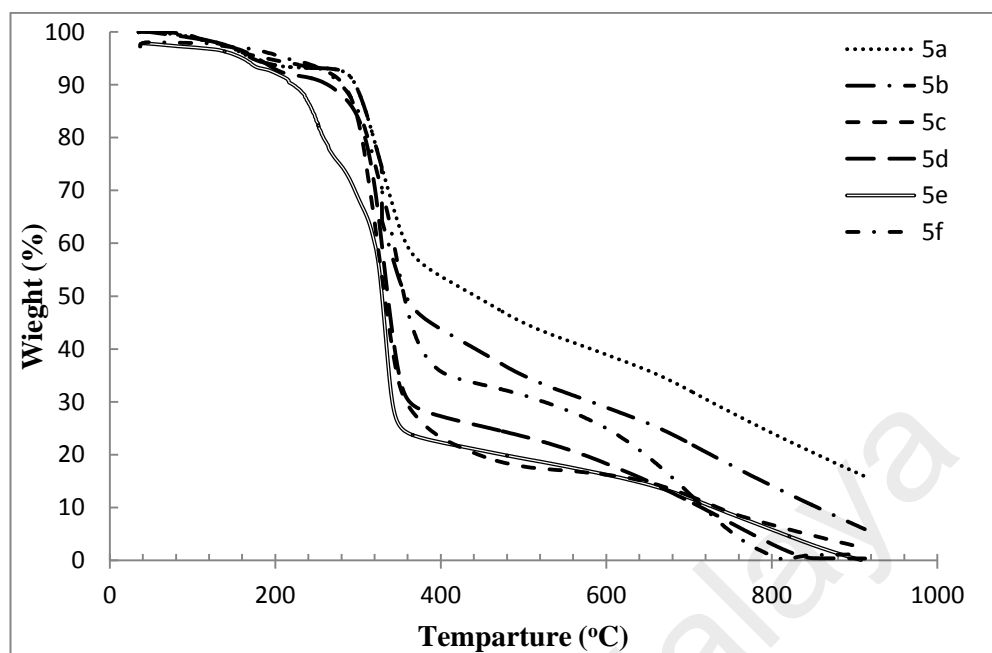
Figure 4.4: Ramped temperature TGA trace curves of imidazolium based geminal dicationic ILs
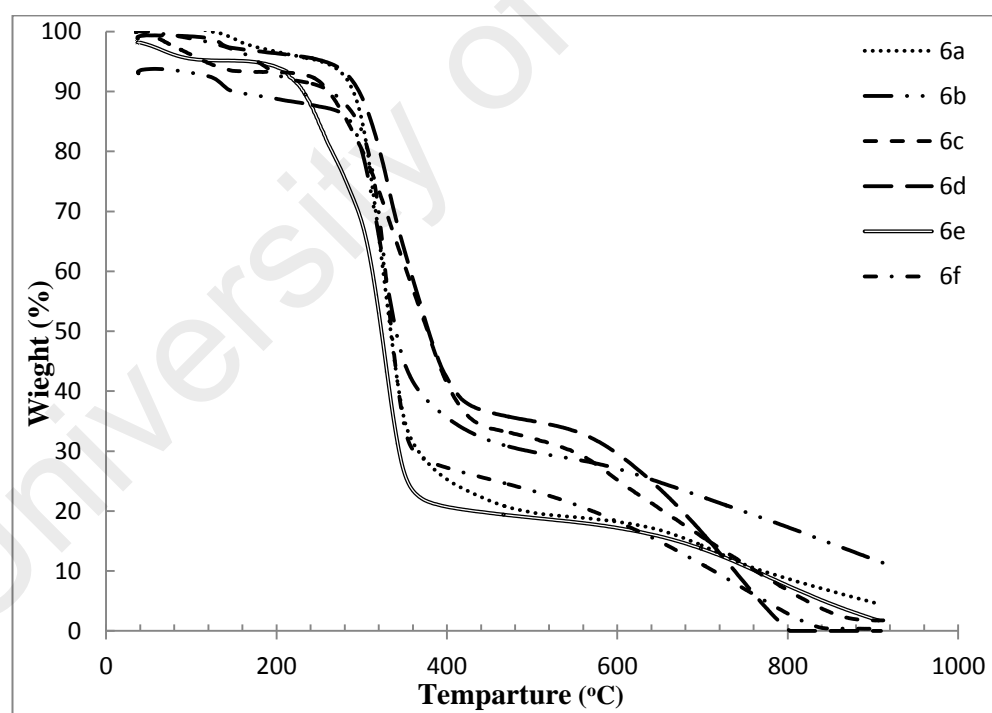
Figure 4.5: Ramped temperature TGA trace curves of benzimidazolium based geminal dicationic ILs

Thermal stability of ILs does not strongly rely on the cations structure (Huddleston *et al.*, 2001; Tao *et al.*, 2014; Tokuda, Hayamizu, Ishii, Susan, & Watanabe, 2005).

Since the prepared geminal dicationic ILs differ only in the cationic substituents of the active side groups on the imidazolium and benzimidazolium rings, minor differences are observed in the decomposition temperatures of these ILs. For example, based on TGA results, T_{onset} varies between 223°C–294°C for **6e** and **5c**, respectively, with approximate weight loss of 10–50%.

4.3 EXPERIMENTAL

4.3.1 General

Allyl bromide (99%), propargyl bromide solution (80% wt with toluene), chloroacetonitrile (99%), 2-bromoethanol (95%), ethyl bromoacetate (98%) and *tert*-butyl bromoacetate (98%) were purchased from Aldrich and used without further purification. All ILs were kept in fridge (5 °C) and freezer (–18 °C) for further evaluation of their properties. General grade solvents were purchased from commercial suppliers and they were used without further purification. The synthesis of compounds **2**, **3** and **4** were described and reported in previous work (Al-Mohammed *et al.*, 2013). The IR spectra were obtained with a Perkin Elmer 400 Fourier Transform Infrared (FTIR) spectrometer. Both ^{1}H and ^{13}C-NMR spectra were recorded on Jeol Lambda and ECA-DELTA as well as Bruker spectrometers at 400 MHz while ^{19}F-NMR was recorded using Bruker spectrometers 400 MHz. High-resolution mass spectra were recorded on Agilent Technologies 6530 Accurate Q-TOF LC–MS system, applying DMSO /MeOH eluents for ILs sample compounds while Agilent 5975 system for EI/MS (Mass Spectra Service Centre of the National University of Singapore) for the rest of the compounds. Thermogravimetric analysis (TGA) measurements were performed using Perkin Elmer TGA4000 based on heating rate of 10 °C min^{-1} under nitrogen atmosphere. Thin layer chromatography was carried out on pre-coated silica gel plates (0.25 mm, 20 × 20 cm, 60F254, E. Merck).

4.3.2 Synthesis of *N*,*N*-Bis[(3-allyl-imidazol-1-iumyl)ethyl]-4-methylbenzenesulph-onamide bromide (5a)

A solution of allyl bromide (2 g, 1.44 mL, 16.7 mmol) in acetonitrile anhydrous (5mL) was added drop-wise to a stirred solution of *N*,*N*-bis[(imidazol-1-yl)ethyl]-4-methylbenzenesulphonamide (compound **3**) (3 g, 8.35 mmol) in acetonitrile anhydrous (15 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was vigorously stirred for 3 h and refluxed at 50-55 °C for 2-3 days. The acetonitrile top layer was decanted and the IL was washed with diethyl ether (3 × 10 mL), then residual solvent was removed *in vacuo*. The product was dried at (40 °C, 0.01 mmHg) for 48 h to provide a viscous hygroscopic syrup in 95% yield (4.8 g). Molecular Formula: $C_{23}H_{31}Br_2N_5O_2S$; Mol. Wt.: 601.40; FTIR (cm^{-1}) 3,059 (C-H)$_{Ar}$, 2,977 (C-H)$_{Aliph}$, 1,644 (C=N)$_{Ar}$, 1,561, 1,493 (C=C)$_{Ar}$, 1,336, 1,156 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.43 (bt~s, 2H, C-H$_{Imidazole}$), 7.94 (t, *J*=1.71 Hz, 2H, C-H$_{Imidazole}$), 7.75 (t, *J*=1.71 Hz, 2H, C-H$_{Imidazole}$), 7.65 (d, *J* = 8.05 Hz, 2H, C-H$_{Ar}$), 7.40 (d, *J* = 8.05 Hz, 2H, C-H$_{Ar}$), 6.08–5.98 (m, 2H, C-H$_{Allyl}$), 5.36 (d, *J*=1.22 Hz, 1H, C-H$_{(1a)Allyl}$), 5.34 (d, *J*=1.22 Hz, 1H, C-H$_{(1b)Allyl}$), 5.33 (d, *J*=1.22 Hz, 1H, C-H$_{(2a)Allyl}$), 5.29 (d, *J*=1.220 Hz, 1H, C-H$_{(2b)Allyl}$), 4.88 (d, *J*= 5.85 Hz, 4H, 2 × (α-CH$_2$)$_{Allyl}$), 4.50 (t, *J* = 6.59 Hz, 4H, 2 × CH$_2$-N), 3.71 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N), 2.39 (s, 3H, (CH$_3$)$_{Ts}$)); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm 143.89 (C$_{Ar}$-S), 136.59 (2 × CH$_{Imidazole}$), 134.89 (C$_{Ar}$-CH$_3$), 131.58 (2 × (CH)$_{Allyl}$, 129.95 (2 × CH$_{Ar}$), 126.98 (2 × CH$_{Imidazole}$), 123.05 (2 × CH$_{Ar}$), 122.30 (2 × CH$_{Imidazole}$), 120.10 (2 × (CH$_2$)$_{Allyl}$, 50.80 (2 × (α-CH$_2$)$_{Allyl}$), 47.90 (2 × CH$_2$-N), 47.12 (2 × CH$_2$-N$_{Ar}$), 20.97 (CH$_3$)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−2Br$^-$ calcd. for $C_{23}H_{30}N_5O_2S^{3+}$: 440.2120, found: 440.2126.

4.3.3 Synthesis of *N*,*N*-Bis[(3-propargyl-imidazol-1-iumyl)ethyl]-4-methylbenzene-sulphonamide bromide (5b)

This compound was prepared analogously to **5a** using *N*,*N*-bis[(imidazol-1-yl)ethyl]-4-methylbenzene-sulphonamide (compound **3**) (3 g, 8.35 mmol) and propargyl bromide

solution 80% wt in toluene (4.96 g, 3.72 mL, 33.4 mmol) to provide a viscous hygroscopic syrup in 98% yield (4.9 g). Molecular Formula: $C_{23}H_{27}Br_2N_5O_2S$; Mol. Wt.: 597.37; FTIR (cm^{-1}) 3,051 (C-H)$_{Ar}$, 2,926, 2,850 (C-H)$_{Aliph}$, 2,125 (C≡C), 1,613(C=N)$_{Ar}$, 1,562, 1,486 (C=C)$_{Ar}$, 1,331, 1,154 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.40 (bt~s, 2H, C-H$_{Imidazole}$), 7.89 (t, J = 1.81 Hz, 2H, C-H$_{Imidazole}$), 7.80 (t, J = 1.81 Hz, 2H, C-H$_{Imidazole}$), 7.63 (d, J = 8.15 Hz, 2H, C-H$_{Ar}$), 7.40 (d, J = 8.15 Hz, 2H, C-H$_{Ar}$), 5.23 (d, J = 2.72 Hz, 4H, 2 × (α-CH$_2$)$_{Propargyl}$), 4.48 (t, J = 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.88 (t, J= 2.72 Hz, 2H, (C-H)$_{Propargyl}$), 3.69 (t, J = 6.34 Hz, 4H, 2 × CH$_2$-N), 2.40 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 144.04 (C$_{Ar}$-S), 136.56 (2 × CH$_{Imidazole}$), 134.87 (C$_{Ar}$-CH$_3$), 130.01 (2 × CH$_{Ar}$), 127.02 (2 × CH$_{Imidazole}$), 123.33 (2 × CH$_{Ar}$), 122.18 (2 × CH$_{Imidazole}$), 79.21 (2 × C$_{Propargyl}$), 75.94 (2 × CH$_{Propargyl}$), 47.72 (2 × CH$_2$-N), 47.23 (2 × CH$_2$-N$_{Ar}$), 38.69 (2 × (α-CH$_2$)$_{Propargyl}$), 21.03 (CH$_3$)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−2Br$^-$ calcd. for $C_{23}H_{25}N_5O_2S^{3+}$: 436.1807, found: 436.1810.

4.3.4 Synthesis of *N,N*-Bis[(3-(cyanomethyl)-imidazol-1-iumyl)ethyl]-4-methylben-zenesulphonamide chloride (5c)

This compound was prepared analogously to **5a** using *N,N*-bis[(imidazol-1-yl)ethyl]-4-methylbenzene-sulphonamide (compound **3**) (3 g, 8.35 mmol) and chloroacetonitrile (1.25 g, 1.05 mL, 16.7 mmol) to provide a viscous hygroscopic liquid in 98% yield (4.2 g). Molecular Formula: $C_{21}H_{25}Cl_2N_7O_2S$; Mol. Wt.: 510.44; FTIR (cm^{-1}) 3,065 (C-H)$_{Ar}$, 2,978 (C-H)$_{Aliph}$, 2,238 (C≡N), 1,629, 1,596 (C=N)$_{Ar}$, 1,563, 1,493 (C=C)$_{Ar}$, 1,336, 1,155 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.88 (bt~s, 2H, C-H$_{Imidazole}$), 8.17 (t, J=1.83 Hz, 2H, C-H$_{Imidazole}$), 8.02 (t, J=1.83 Hz, 2H, C-H$_{Imidazole}$), 7.67 (d, J = 8.24 Hz, 2H, C-H$_{Ar}$), 7.39 (d, J = 8.24 Hz, 2H, C-H$_{Ar}$), 5.90 (s, 4H, 2 × (α-CH$_2$)), 4.61 (t, J = 6.10 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.71 (t, J= 6.10 Hz, 4H, 2 × CH$_2$-N), 2.38 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 144.03 (C$_{Ar}$-S), 137.90 (2 × CH$_{Imidazole}$), 134.56 (C$_{Ar}$-CH$_3$), 130.00 (2 × CH$_{Ar}$), 127.16 (2 × CH$_{Ar}$), 123.67 (2 × CH$_{Imidazole}$), 122.49 (2 × CH$_{Imidazole}$), 114.73 (2 × CN), 48.20 (2 × CH$_2$-N), 47.58 (2 ×

CH$_2$-N$_{Ar}$), 36.79 (2 × (α-CH$_2$)), 21.02 (CH$_3$)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−2Cl$^-$ calcd. for C$_{21}$H$_{24}$N$_7$O$_2$S^{3+}: 438.1712, found: 438.1715.

4.3.5   *N,N*-Bis[(3-(2-ethanolyl)-imidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide (5d)

This compound was prepared analogously to **5a** using *N,N*-bis[(imidazol-1-yl)ethyl]-4-methylbenzene-sulphonamide (compound **3**) (3 g, 8.35 mmol) and 2-bromoethanol (3.13 g, 1.77 mL, 25.1 mmol) to provide viscous hygroscopic liquid in 99% yield (5 g). Molecular Formula: C$_{21}$H$_{31}$Br$_2$N$_5$O$_4$S; Mol. Wt.: 609.37; FTIR (cm^{-1}) 3,288 (O-H), 3,139, 3,071 (C-H)$_{Ar}$, 2,954, 2,876 (C-H)$_{Aliph}$, 1,596 (C=N)$_{Ar}$, 1,562, 1,493 (C=C)$_{Ar}$, 1,335, 1,155 (O=S=O), 1,066 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 9.25 (bt~s, 2H, C-H$_{Imidazole}$), 7.80 (t, *J*=1.81 Hz, 2H, C-H$_{Imidazole}$), 7.69 (t, *J*=1.81 Hz, 2H, C-H$_{Imidazole}$), 7.63 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 7.36 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 5.16 (bs, 2H, 2 × O-H), 4.41 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 4.19 (t, *J*= 4.98 Hz, 4H, 2 × (α-CH$_2$)), 3.69 (t, *J*= 4.98 Hz, 4H, 2 × C$\underline{H}_2$-OH), 3.64 (t, overlap, 4H, 2 × CH$_2$-N), 2.35 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 144.13 (C$_{Ar}$-S), 136.79 (2 × CH$_{Imidazole}$), 134.79 (C$_{Ar}$-CH$_3$), 130.11 (2 × CH$_{Ar}$), 127.17 (2 × CH$_{Ar}$), 122.75 (2 × CH$_{Imidazole}$), 122.67 (2 × CH$_{Imidazole}$), 59.37 (2 × $\underline{C}$H$_2$-OH), 51.76 (2 × (α-CH$_2$)), 48.04 (2 × CH$_2$-N), 47.16 (2 × CH$_2$-N$_{Ar}$), 21.11 (CH$_3$)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−2Br$^-$ calcd. for C$_{21}$H$_{30}$N$_5$O$_4$S^{3+}: 448.2019, found: 448.2061.

4.3.6   Synthesis   of   *N,N*-Bis[(3-(2-ethoxy-2-oxoethyl)-imidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide (5e)

This compound was prepared analogously to **5a** using *N,N*-bis[(imidazol-1-yl)ethyl]-4-methylbenzene-sulphonamide (compound **3**) (3 g, 8.35 mmol) and ethyl bromoacetate (2.79 g, 1.86 mL, 16.7 mmol) to provide a white hygroscopic semi-solid in 96% yield (5.5 g). Molecular Formula: C$_{25}$H$_{35}$Br$_2$N$_5$O$_6$S; Mol. Wt.: 693.45; FTIR (cm^{-1}) 3,069 (C-H)$_{Ar}$, 2,982 (C-H)$_{Aliph}$, 1,742 (C=O), 1,627, 1,596 (C=N)$_{Ar}$, 1564 1,493, 1,449 (C=C)$_{Ar}$, 1,339 1,156 (O=S=O), 1,088 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 9.40 (bt~s,

2H, C-H$_{\text{Imidazole}}$), 7.95 (t, J = 1.71 Hz, 2H, C-H$_{\text{Imidazole}}$), 7.80 (t, J = 1.71 Hz, 2H, C-H$_{\text{Imidazole}}$), 7.68 (d, J = 8.29 Hz, 2H, C-H$_{\text{Ar}}$), 7.41 (d, J = 8.05 Hz, 2H, C-H$_{\text{Ar}}$), 5.34 (s, 4H, 2 × (α-CH$_2$)), 4.53 (t, J = 6.34 Hz, 4H, 2 × CH$_2$-N$_{\text{Ar}}$), 4.20 (q, J= 7.07 Hz, 4H, 2 × O-CH$_2$-), 3.67 (t, J = 6.34 Hz, 4H, 2 × CH$_2$-N), 2.40 (s, 3H, (CH$_3$)$_{\text{Ts}}$), 1.23 (t, J= 7.07 Hz, 6H, 2 × (-CH$_3$)); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.69 (2 × C=O), 144.00 (C$_{\text{Ar}}$-S), 137.63 (2 × CH$_{\text{Imidazole}}$), 134.38 (C$_{\text{Ar}}$-CH$_3$), 129.98 (2 × CH$_{\text{Ar}}$), 127.16 (2 × CH$_{\text{Imidazole}}$), 123.65 (2 × CH$_{\text{Ar}}$), 122.55 (2 × CH$_{\text{Imidazole}}$), 61.86 (2 × $\underline{\text{C}}$H$_2$-O), 49.57 (2 × (α-CH$_2$)), 48.16 (2 × CH$_2$-N,), 47.43 (2 × CH$_2$-N$_{\text{Ar}}$), 20.98 (CH$_3$)$_{\text{Ts}}$, 13.92 (2 × (CH$_3$)); HRMS: m/z, [M^{+2}–H]−2Br$^-$ calcd. for C$_{25}$H$_{34}$N$_5$O$_6$S^{3+} : 532.2230, found: 532.2234

4.3.7 Synthesis of *N,N*-Bis[(3-(2-tert-butoxy-2-oxoethyl)-imidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide (5f)

This compound was prepared analogously to **5a** using *N,N*-bis[(imidazol-1-yl)ethyl]-4-methylbenzene-sulphonamide (compound **3**) (3 g, 8.35 mmol) and *tert*-butyl bromoacetate (3.26 g, 2.43 mL, 16.7 mmol) to provide a white hygroscopic semi-solid in 95% yield (5.9 g). Molecular Formula: C$_{29}$H$_{43}$Br$_2$N$_5$O$_6$S; Mol. Wt.: 749.55; FTIR (cm^{-1}) 3,063 (C-H)$_{\text{Ar}}$, 2,980 (C-H)$_{\text{Aliph}}$, 1,743 (C=O) 1,597 (C=N)$_{\text{Ar}}$, 1,566, 1,443 (C=C)$_{\text{Ar}}$, 1,364, 1,155 (O=S=O), 1,042 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.35 (bt~s, 2H, C-H$_{\text{Imidazole}}$), 7.90 (t, J = 1.71 Hz, 2H, C-H$_{\text{Imidazole}}$), 7.76 (t, J = 1.71 Hz, 2H, C-H$_{\text{Imidazole}}$), 7.68 (d, J = 8.29 Hz, 2H, C-H$_{\text{Ar}}$), 7.41 (d, J = 8.29 Hz, 2H, C-H$_{\text{Ar}}$), 5.22 (s, 4H, 2 × (α-CH$_2$)), 4.51 (t, J = 6.34 Hz, 4H, 2 × CH$_2$-N$_{\text{Ar}}$), 3.66 (t, J = 6.34 Hz, 4H, 2 × CH$_2$-N), 2.40 (s, 3H, (-CH$_3$)$_{\text{Ts}}$), 1.45 (s, 18H, 6 × (-CH$_3$)); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 165.71 (2 × C=O), 144.06 (C$_{\text{Ar}}$-S), 137.66 (2 × CH$_{\text{Imidazole}}$), 134.46 (C$_{\text{Ar}}$-CH$_3$), 130.02 (2 × CH$_{\text{Ar}}$), 127.18 (2 × CH$_{\text{Ar}}$), 123.70 (2 × CH$_{\text{Imidazole}}$), 122.49 (2 × CH$_{\text{Imidazole}}$), 83.06 (2 × C), 50.04 (2 × (α-CH$_2$)), 48.09 (2 × CH$_2$-N), 47.37 (2 × CH$_2$-N$_{\text{Ar}}$), 27.64 (6 × CH$_3$), 21.02 (CH$_3$)$_{\text{Ts}}$; HRMS: m/z, [M^{+2}–H]−2Br$^-$ calcd. for C$_{29}$H$_{42}$N$_5$O$_6$S^{3+} : 588.2856, found: 588.2913.

4.3.8 Synthesis of *N,N*-Bis[(3-allyl-benzimidazol-1-iumyl)ethyl]-4-methylbenzene-sulphonamide bromide (6a)

This compound was prepared analogously to **5a** using *N,N*-bis[(benzimidazol-1-yl)ethyl]-4-methyl-benzenesulphonamide (compound **4**) (4 g, 8.7 mmol) and chloroacetonitrile 99% (2.11 g, 1.51 mL, 17.4 mmol) to provide a viscous hygroscopic liquid in 95% yield (5.8 g). Molecular Formula: $C_{31}H_{35}Br_2N_5O_2S$; Mol. Wt.: 701.51; FTIR (cm^{-1}): 3,133 3,027 (C-H)$_{Ar}$, 2,928 (C-H)$_{Aliph}$, 1,615, 1,596 (C=N)$_{Ar}$, 1,562, 1,485 (C=C)$_{Ar}$, 1,331, 1,154 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 10.09 (s, 2H, C-H$_{BImidazole}$), 8.15–8.13 (m, 2H, C-H$_{BImidazole}$), 8.00–7.96 (m, 2H, C-H$_{BImidazole}$), 7.71–7.65 (m, 4H, CH$_{BImidazole}$), 7.36 (d, *J* = 8.29 Hz, 2H, C-H$_{Ar}$), 7.11 (d, *J* = 8.29 Hz, 2H, C-H$_{Ar}$), 6.15–6.05 (m, 2H, C-H$_{Allyl}$), 5.47 (d, *J*=1.22 Hz, 1H, C-H$_{(1a)Allyl}$), 5.43 (d, *J*=1.22 Hz, 1H, C-H$_{(1b)Allyl}$), 5.40 (d, *J*=0.98 Hz, 1H, C-H$_{(2a)Allyl}$), 5.37 (d, *J*=0.98 Hz,1H, C-H$_{(2b)Allyl}$), 5.24 (d, *J*= 5.61 Hz, 4H, 2 × (α-CH$_2$)$_{Allyl}$), 4.90 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.96 (t, *J* = 6.10 Hz, 4H, 2 × CH$_2$-N), 2.27 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 143.65 (C$_{Ar}$-S), 142.62 (2 × CH$_{BImidazole}$), 134.97 (C$_{Ar}$-CH$_3$), 131.16 (2 × C$_{BImidazole}$), 130.77 (2 × (CH)$_{Allyl}$, 130.75 (2 × C$_{BImidazole}$), 129.55 (2 × CH$_{BImidazole}$), 126.67 (2 × CH$_{BImidazole}$), 126.52 (2 × CH$_{Ar}$), 126.42 (2 × CH$_{Ar}$), 120.47 (2 × (CH$_2$)$_{Allyl}$), 113.82 (2 × CH$_{BImidazole}$), 113.60 (2 × CH$_{BImidazole}$), 48.74 (2 × (α-CH$_2$)$_{Allyl}$, 46.19 (2 × CH$_2$-N), 44.82 (2 × CH$_2$-N$_{Ar}$), 20.95 (CH$_3$)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−2Br$^-$ calcd. for $C_{31}H_{34}N_5O_2S^{3+}$: 540.2433, found: 540.2470.

4.3.9 Synthesis of *N,N*-Bis[(3-propargyl-benzimidazol-1-iumyl)ethyl]-4-methyl-benzenesulphonamide bromide (6b)

This compound was prepared analogously to **5a** using *N,N*-bis[(benzimidazol-1-yl)ethyl]-4-methyl- benzenesulphonamide (compound **4**) (4 g, 8.7 mmol) and propargyl bromide solution 80% wt in toluene (5.18 g, 3.88 mL, 33.8 mmol) to provide a viscous hygroscopic syrup 98% yield (6 g). Molecular Formula: $C_{31}H_{31}Br_2N_5O_2S$; Mol. Wt.: 697.48; FTIR (cm^{-1}): 3,152 (C-H)$_{Ar}$, 2,960 (C-H)$_{Aliph}$, 2,121 (C≡C), 1,613, 1,596 (C=

N)$_{Ar}$, 1,562, 1,486 (C=C)$_{Ar}$, 1,331, 1,154 (O=S=O), 1,070 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.02 (s, 2H, C-H$_{BImidazole}$), 8.13–8.09 (m, 2H, C-H$_{BImidazole}$), 8.05–8.00 (m, 2H, C-H$_{BImidazole}$), 7.76–7.70 (m, 4H, CH$_{BImidazole}$), 7.34 (d, J = 8.15 Hz, 2H,C-H$_{Ar}$), 7.10 (d, J = 8.15 Hz, 2H, C-H$_{Ar}$), 5.58 (d, J = 2.72 Hz, 4H, 2 × (α-CH$_2$)$_{Propargyl}$), 4.87 (t, J= 5.89 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.95 (t, Overlap, 4H, 2 × CH$_2$-N), 3.91 (t, J= 2.27 Hz, 2H, (C-H)$_{Propargyl}$), 2.26 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 143.78 (C$_{Ar}$-S), 142.46 (2 × CH$_{BImidazole}$), 134.70 (C$_{Ar}$-CH$_3$), 131.18 (2 × C$_{BImidazole}$), 130.36 (2 × C$_{BImidazole}$), 129.61 (2 × CH$_{Ar}$), 126.99 (2 × CH$_{Ar}$), 126.85 (2 × CH$_{BImidazole}$), 126.45 (2 × CH$_{BImidazole}$), 113.76 (4 × CH$_{BImidazole}$), 79.43 (2 × C$_{Propargyl}$), 75.42 (2 × CH$_{Propargyl}$), 45.99 (2 × CH$_2$-N), 44.90 (2 × CH$_2$-N$_{Ar}$), 36.77 (2 × (α-CH$_2$)$_{Propargyl}$), 20.99 (CH$_3$)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−2Br$^−$ calcd. for C$_{31}$H$_{30}$N$_5$O$_2$S^{3+} : 536.2120, found: 536.2048.

4.3.10 Synthesis of *N,N*-Bis[(3-(cyanomethyl)-benzimidazol-1-iumyl)ethyl]-4-meth-ylbenzenesulphonamide chloride (6c)

This compound was prepared analogously to **5a** using *N,N*-bis[(benzimidazol-1-yl)ethyl]-4-methyl-benzenesulphonamide (compound **4**) (4 g, 8.7 mmol) and chloroacetonitrile (1.3 g, 1.09 mL, 17.4 mmol) to provide a viscous hygroscopic syrup in 94% yield (5 g). Molecular Formula: C$_{29}$H$_{29}$Cl$_2$N$_7$O$_2$S; Mol. Wt.: 610.56; FTIR (cm^{-1}): 3,095, 3,050 (C-H)$_{Ar}$, 2,969 (C-H)$_{Aliph}$, 2,235 (C≡N), 1,614, 1,596 (C=N)$_{Ar}$, 1,563, 1,487 (C=C)$_{Ar}$, 1,329, 1,155 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.31 (s, 2H, C-H$_{BImidazole}$), 8.19–8.09 (m, 4H, C-H$_{BImidazole}$), 7.81–7.71 (m, 4H, C-H$_{BImidazole}$), 7.39 (d, J = 8.15 Hz, 2H, C-H$_{Ar}$), 7.13 (d, J = 8.15 Hz, 2H, C-H$_{Ar}$), 6.13 (s, 2H, (α-CH$_2$)), 4.95 (t, J= 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.89 (t, J= 6.34 Hz, 4H, 2 × CH$_2$-N), 2.26 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 143.92 (C$_{Ar}$-S), 143.83 (2 × CH$_{BImidazole}$), 134.37 (C$_{Ar}$-CH$_3$), 130.95 (2 × C$_{BImidazole}$), 130.27 (2 × C$_{BImidazole}$), 129.66 (2 × CH$_{Ar}$), 127.32 (2 × CH$_{Ar}$), 127.24 (2 × CH$_{BImidazole}$), 126.66 (2 × CH$_{BImidazole}$),

114.17 ($2 \times CH_{BImidazole}$), 114.05 ($2 \times CH_{BImidazole}$), 113.34 ($2 \times CN$), 46.51 ($2 \times CH_2$-N), 45.35 ($2 \times CH_2$-N_{Ar}), 34.88 ($2 \times$ (α-CH_2)), 20.96 (CH_3)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−$2Cl^-$ calcd. for $C_{29}H_{28}N_7O_2S^{3+}$: 538.2025, found: 538.2077.

4.3.11 Synthesis of *N,N*-Bis[(3-(2-ethanolyl)-benzimidazol-1-iumyl)ethyl]-4-methyl-benzenesulphonamide bromide (6d)

This compound was prepared analogously to **5a** using *N,N*-bis[(benzimidazol-1-yl)ethyl]-4-methyl-benzenesulphonamide (compound **4**) (4 g, 8.7 mmol) and 2-bromoethanol (3.26 g, 1.84 mL, 26.1 mmol) to provide a viscous hygroscopic liquid in 98% yield (6 g). Molecular Formula: $C_{29}H_{35}Br_2N_5O_4S$; Mol. Wt.: 709.49; FTIR (cm^{-1}): 3,312 (O-H), 3,137, 3,027 (C-H)$_{Ar}$, 2,982 (C-H)$_{Aliph}$, 1,614, 1,596 (C=N)$_{Ar}$, 1,563, 1,485 (C=C)$_{Ar}$, 1,330, 1,154 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.85 (s, 2H, C-H$_{BImidazole}$), 8.09–8.05 (m, 4H, C-H$_{BImidazole}$), 7.71–7.66 (m, 4H, C-H$_{BImidazole}$), 7.34 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 7.08 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 5.22 (bs, 2H, $2 \times$ O-H), 4.84 (t, *J*= 6.34 Hz, 4H, $2 \times CH_2$-N_{Ar}), 4.57 (t, *J*= 4.98 Hz, 4H, $2 \times$ (α-CH_2)), 3.90 (t, *J* = 6.34 Hz, 4H, $2 \times CH_2$-N), 3.83 (bt~s, 4H, $2 \times$ <u>C</u>H_2-OH), 2.27 (s, 3H, (CH_3)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 143.76 (C_{Ar}-S), 142.81 ($2 \times CH_{BImidazole}$), 134.72 (C_{Ar}-CH_3), 131.22 ($2 \times C_{BImidazole}$), 131.02 ($2 \times C_{BImidazole}$), 129.69 ($2 \times CH_{Ar}$), 129.59 ($2 \times CH_{Ar}$), 126.65 ($2 \times CH_{BImidazole}$), 126.50 ($2 \times CH_{BImidazole}$), 113.99 ($2 \times CH_{BImidazole}$), 113.44 ($2 \times CH_{BImidazole}$), 58.68 ($2 \times CH_2$-OH), 49.48 ($2 \times$ (α-CH_2)), 46.08 ($2 \times CH_2$-N), 44.68 ($2 \times CH_2$-N_{Ar}), 21.05 (CH_3)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−$2Br^-$ calcd. for $C_{29}H_{34}N_5O_4S^{3+}$: 548.2332, found: 548.2394.

4.3.12 Synthesis of *N,N*-Bis[(3-(2-ethoxy-2-oxoethyl)-benzimidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide (6e)

This compound was prepared analogously to **5a** using *N,N*-bis[(benzimidazol-1-yl)ethyl]-4-methyl-benzenesulphonamide (compound **4**) (4 g, 8.7 mmol) and ethyl bromoacetate (2.9 g, 1.93 mL, 17.4 mmol) to provide a viscous hygroscopic syrup in 98% yield (6.8 g). Molecular Formula: $C_{33}H_{39}Br_2N_5O_4S$; Mol. Wt.: 793.57; FTIR (cm^{-1}

): 3,059 (C-H)$_{Ar}$, 2,977 (C-H)$_{Aliph}$, 1,741 (C=O), 1,614, 1,596 (C=N)$_{Ar}$, 1,564 1,485, (C=C)$_{Ar}$, 1,339 1,155 (O=S=O), 1,088 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.98 (s, 2H, C-H$_{BImidazole}$), 8.13–8.10 (m, 2H, C-H$_{BImidazole}$), 8.06–8.03 (m, 2H, C-H$_{BImidazole}$), 7.73–7.68 (m, 4H, CH$_{BImidazole}$), 7.41 (d, J = 8.54 Hz, 2H, C-H$_{Ar}$), 7.12 (d, J = 8.24 Hz, 2H, C-H$_{Ar}$), 5.69 (s, 4H, 2 × (α-CH$_2$)), 4.91 (t, J= 6.10 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 4.22 (q, J= 7.23 Hz, 4H, 2 × O-CH$_2$-), 3.89 (t, J= 6.10 Hz, 4H, 2 × CH$_2$-N), 2.27 (s, 3H, -(CH$_3$)$_{Ts}$), 1.24 (t, J= 7.32 Hz, 6H, 2 × (-CH$_3$)); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.51 (2 × C=O), 143.89 (C$_{Ar}$-S), 143.53 (2 × CH$_{BImidazole}$), 134.34 (C$_{Ar}$-CH$_3$), 131.33 (2 × C$_{BImidazole}$), 130.57 (2 × C$_{BImidazole}$), 129.64 (2 × CH$_{Ar}$), 126.90 (2 × CH$_{Ar}$), 126.85 (2 × CH$_{BImidazole}$), 126.69 (2 × CH$_{BImidazole}$), 113.95 (2 × CH$_{BImidazole}$), 113.65 (2 × CH$_{BImidazole}$), 62.08 (2 × $\underline{C}$H$_2$-O), 47.48 (2 × CH$_2$-N), 46.30 (2 × (α-CH$_2$)), 45.19 (2 × CH$_2$-N$_{Ar}$), 20.99 (CH$_3$)$_{Ts}$, 13.96 (CH$_3$) ; HRMS: m/z, [M^{+2}–H]−2Br$^-$ calcd. for C$_{33}$H$_{38}$N$_5$O$_6$S^{3+} : 632.2543, found: 632.2601.

4.3.13 Synthesis of *N,N*-Bis[(3-(2-tert-butoxy-2-oxoethyl)-benzimidazol-1-iumyl)-ethyl]-4-methylbenzenesulphonamide bromide (6f)

This compound was prepared analogously to **5a** using *N,N*-bis[(benzimidazol-1-yl)ethyl]-4-methyl- benzenesulphonamide (compound **4**) (4 g, 8.7 mmol) and *tert*-butyl bromoacetate (3.4 g, 2.54 mL, 17.4 mmol) to provide a viscous hygroscopic syrup in 98% yield (7.25 g). Molecular Formula: C$_{37}$H$_{47}$Br$_2$N$_5$O$_6$S; Mol. Wt.: 849.67; FTIR (cm^{-1}): 3,065, (C-H)$_{Ar}$, 2,979 (C-H)$_{Aliph}$, 1,739 (C=O), 1,597 (C=N)$_{Ar}$, 1,564, 1,488 (C=C)$_{Ar}$, 1,364, 1,151 (O=S=O), 1,088 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.95 (s, 2H, C-H$_{BImidazole}$), 8.12–8.08 (m, 2H, C-H$_{BImidazole}$), 8.04–8.00 (m, 2H, C-H$_{BImidazole}$), 7.73–7.68 (m, 4H, CH$_{BImidazole}$), 7.41 (d, J = 8.15 Hz, 2H, C-H$_{Ar}$), 7.11 (d, J = 8.15 Hz, 2H, C-H$_{Ar}$), 5.58 (s, 4H, 2 × (α-CH$_2$)), 4.90 (t, J= 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.88 (t, J= 6.12 Hz, 4H, 2 × CH$_2$-N), 2.26 (s, 3H, (-CH$_3$)$_{Ts}$), 1.43 (s, 18H, 6 × (-CH$_3$)); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.51 (2 × C=O), 143.97 (C$_{Ar}$-S), 143.53 (2 ×

CH$_{BImidazole}$), 134.42 (C$_{Ar}$-CH$_3$), 131.39 (2 × C$_{BImidazole}$), 130.60 (2 × C$_{BImidazole}$), 129.67 (2 × CH$_{Ar}$), 126.96 (2 × CH$_{Ar}$), 126.90 (2 × CH$_{BImidazole}$), 126.79 (2 × CH$_{BImidazole}$), 113.92 (2 × CH$_{BImidazole}$), 113.64 (2 × CH$_{BImidazole}$), 83.42 (2 × C), 47.97 (2 × (α-CH$_2$)), 46.31 (2 × CH$_2$-N), 45.15 (2 × CH$_2$-N$_{Ar}$), 27.66 (6 × CH$_3$), 21.06 (CH$_3$)$_{Ts}$; HRMS: m/z, [M^{+2}–H]−2Br$^−$ calcd. for C$_{37}$H$_{46}$N$_5$O$_6$S^{3+} : 688.3169, found: 688.3217.

4.3.14 Synthesis of *N,N*-Bis[(3-(2-ethanolyl)-imidazol-1-iumyl)ethyl]-4-methylbenz-enesulphonamide bis(trifluoromethylsulphonyl)amide (7d)

A flask was charged with *N,N*-bis[(3-(2-ethanolyl)-imidazol-1-iumyl)ethyl]-4-methyl benzenesulphonamide bromide **5d** (0.6 g, 1.0 mmol) and de-ionized water (10 mL). Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (0.72 g, 2.5 mmol) in de-ionized water (3 mL) was added in one portion and the suspension was stirred vigorously for 7 h at room temperature. The mixture was extracted with ethyl acetate (3×5mL) after stirring for 1h each time. The combined organic layers were evaporated on the rotary evaporator and under high vacuum for 8 h to remove the solvent and provide a clear viscous hygroscopic liquid at room temperature in 83% yield (0.83 g). Molecular Formula: C$_{25}$H$_{31}$F$_{12}$N$_7$O$_{12}$S$_5$; Mol. Wt.: 1,009.85; FTIR (cm^{-1}) 3,280 (O-H), 3,131, 3,068 (C-H)$_{Ar}$, 2,958, 2,875 (C-H)$_{Aliph}$, 1,585 (C=N)$_{Ar}$, 1,548, 1,483 (C=C)$_{Ar}$, 1,342, 1,218 (C-F), 1,332, 1,151 (O=S=O), 1,075 (C-O), 1,060 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 8.98 (bt~s, 2H, C-H$_{Imidazole}$), 7.78 (t, *J*=1.81 Hz, 2H, C-H$_{Imidazole}$), 7.67 (t, *J*=1.81 Hz, 2H, C-H$_{Imidazole}$), 7.61 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 7.35 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 5.15 (bs, 2H, 2 × O-H), 4.41 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 4.20 (t, *J*= 4.98 Hz, 4H, 2 × (α-CH$_2$)), 3.68 (t, *J*= 4.98 Hz, 4H, 2 × CH$_2$-OH), 3.62 (t, 4H, 2 × CH$_2$-N), 2.33 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 144.62 (C$_{Ar}$-S), 136.92 (2 × CH$_{Imidazole}$), 134.87 (C$_{Ar}$-CH$_3$), 130.35 (2 × CH$_{Ar}$), 129.12 (2 × CH$_{Ar}$), 124.44, 121.22, 118.00, 114.78 (q, *J*=322 Hz, CF$_3$), 122.33 (2 × CH$_{Imidazole}$), 121.97 (2 × CH$_{Imidazole}$), 59.31 (2 × C̲H$_2$-OH), 51.90 (2 × (α-CH$_2$), 48.03 (2 × CH$_2$-N), 47.10 (2 ×

CH$_2$-N$_{Ar}$), 21.32 (CH$_3$)$_{Ts}$; ^{19}F (336, MHz) δ ppm: −80.12 (CF$_3$); HRMS: m/z, [M^{+2}−H]−2NTF$_2$$^-$ calcd. for C$_{21}$H$_{30}$N$_5$O$_4$S^{3+} : 448.2019, found: 448.2068; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9144.

4.3.15 Synthesis of *N,N*-Bis[(3-(2-ethoxy-2-oxoethyl)-imidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bis(trifluoromethylsulphonyl)amide (7e)

This compound was prepared analogously to **7d** using *N,N*-bis[(3-(2-ethoxy-2-oxoethyl)-imidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide **5e** (0.7 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (0.72 g, 2.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 96% yield (1.15 g). Molecular Formula: C$_{29}$H$_{35}$F$_{12}$N$_7$O$_{14}$S$_5$; Mol. Wt.: 1,093.93; FTIR (cm^{-1}) 3,072 (C-H)$_{Ar}$, 2,990 (C-H)$_{Aliph}$, 1,748 (C=O), 1,626, 1,590 (C=N)$_{Ar}$, 1,560 1,495, 1,449 (C=C)$_{Ar}$, 1,352 1,156 (O=S=O), 1,344, 1,218 (C-F), 1,075 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 9.13 (bt~s, 2H, C-H$_{Imidazole}$), 7.76 (t, *J* = 1.81 Hz, 2H, C-H$_{Imidazole}$), 7.72 (t, *J* = 1.81 Hz, 2H, C-H$_{Imidazole}$), 7.65 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 7.42 (d, *J* = 8.15 Hz, 2H, C-H$_{Ar}$), 5.26 (s, 4H, 2 × (α-CH$_2$)), 4.42 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 4.22 (q, *J*= 7.25 Hz, 4H, 2 × O-CH$_2$-), 3.61 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N), 2.41 (s, 3H, (CH$_3$)$_{Ts}$), 1.25 (t, *J*= 7.25 Hz, 6H, 2 × (-CH$_3$)); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 166.83 (2 × C=O), 144.18 (C$_{Ar}$-S), 137.66 (2 × CH$_{Imidazole}$), 134.47 (C$_{Ar}$-CH$_3$), 130.04 (2 × CH$_{Ar}$), 127.16 (2 × CH$_{Imidazole}$), 124.34, 121.10, 117.87, 114.63 (q, *J*=322 Hz, CF$_3$), 123.88 (2 × CH$_{Ar}$), 122.61 (2 × CH$_{Imidazole}$), 61.99 (2 × $\underline{C}$H$_2$-O), 49.62 (2 × (α-CH$_2$)), 48.14 (2 × CH$_2$-N), 47.46 (2 × CH$_2$-N$_{Ar}$), 21.00 (CH$_3$)$_{Ts}$, 13.96 (2 × (CH$_3$)$_{BEA}$); ^{19}F (336, MHz) δ ppm: −80.00 (CF$_3$); HRMS: m/z, [M^{+2}−H]−2NTF$_2$$^-$ calcd. for C$_{25}$H$_{34}$N$_5$O$_6$S^{3+}: 532.2230, found: 532.2252; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9205.

4.3.16 Synthesis of *N,N*-Bis[(3-(2-*tert*-butoxy-2-oxoethyl)-imidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bis(trifluoromethylsulphonyl)amide (7f)

This compound was prepared analogously to **7d** using *N,N*-bis[(3-(2-*tert*-butoxy-2-oxoethyl)-imidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide **5f** (0.75 g, 1.0 mmole) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (0.72 g, 2.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 95% yield (1.1 g). Molecular Formula: C$_{33}$H$_{43}$F$_{12}$N$_7$O$_{14}$S$_5$; Mol. Wt.: 1,150.03; FTIR (cm^{-1}) 3,072 (C-H)$_{Ar}$, 2,979, 2,880 (C-H)$_{Aliph}$, 1,743 (C=O), 1,598 (C=N)$_{Ar}$, 1,560, 1,466 (C=C)$_{Ar}$, 1,360, 1,155 (O=S=O), 1,359, 1,218 (C-F), 1,056 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 9.14 (bt~s, 2H, C-H$_{Imidazole}$), 7.75 (t, *J* = 1.95 Hz, 2H, C-H$_{Imidazole}$), 7.70 (t, *J* = 1.91 Hz, 2H, C-H$_{Imidazole}$), 7.65 (d, *J* = 8.29 Hz, 2H, C-H$_{Ar}$), 7.41 (d, *J* = 8.29 Hz, 2H, C-H$_{Ar}$), 5.16 (s, 4H, 2 × (α-CH$_2$)), 4.42 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.61 (t, *J* = 6.34 Hz, 4H, 2 × CH$_2$-N), 2.41 (s, 3H, (-CH$_3$)$_{Ts}$), 1.46 (s, 18H, 6 × (-CH$_3$)); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 165.85 (2 × C=O), 144.22 (C$_{Ar}$-S), 137.68 (2 × CH$_{Imidazole}$), 134.55 (C$_{Ar}$-CH$_3$), 130.09 (2 × CH$_{Ar}$), 127.16 (2 × CH$_{Ar}$), 124.30, 121.08, 117.86, 114.64 (q, *J*=322 Hz, CF$_3$), 123.92 (2 × CH$_{Imidazole}$), 122.55 (2 × CH$_{Imidazole}$), 82.97 (2 × C$_{TBE}$), 50.51 (2 × (α-CH$_2$)), 48.08 (2 × CH$_2$-N), 47.41 (2 × CH$_2$-N$_{Ar}$), 26.94 (6 × CH$_3$), 20.96 (CH$_3$)$_{Ts}$; ^{19}F (336, MHz) δ ppm: −80.50 (CF$_3$); HRMS: m/z, [M^{+2}−H]−2NTF$_2$$^-$ calcd. for C$_{29}$H$_{42}$N$_5$O$_6$S^{3+} : 588.2856, found: 588.2919; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9145.

4.3.17 Synthesis of *N,N*-Bis[(3-allyl-benzimidazol-1-iumyl)ethyl]-4-methylbenzene-sulphonamide bis(trifluoromethylsulphonyl)amide (8a)

This compound was prepared analogously to **7d** using *N,N*-bis[(3-allyl-benzimidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide **6a** (0.7 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (0.72 g, 2.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 90% yield (1 g). Molecular Formula: C$_{35}$H$_{35}$F$_{12}$N$_7$O$_{10}$S$_5$; Mol. Wt.: 1,101.99; FTIR (cm^{-1}): 3,142, 3,027

(C-H)$_{Ar}$, 2,928 (C-H)$_{Aliph}$, 1,615, 1,596 (C=N)$_{Ar}$, 1,562, 1,485 (C=C)$_{Ar}$, 1,342, 1,217 (C-F), 1,331, 1,154 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.74 (s, 2H, C-H$_{BImidazole}$), 8.08–8.05 (m, 2H, C-H$_{BImidazole}$), 7.98–7.93 (m, 2H, C-H$_{BImidazole}$), 7.73–7.66 (m, 4H, CH$_{BImidazole}$), 7.31 (d, J = 7.70 Hz, 2H, C-H$_{Ar}$), 7.08 (d, J = 7.70 Hz, 2H, C-H$_{Ar}$), 6.12–6.02 (m, 2H, C-H$_{Allyl}$), 5.44 (d, J=1.36 Hz, 1H, C-H$_{(1a)Allyl}$), 5.42 (d, J=1.36 Hz, 1H, C-H$_{(1b)Allyl}$), 5.40 (d, J=1.36 Hz, 1H, C-H$_{(2a)Allyl}$), 5.38 (d, J=1.36 Hz, 1H, C-H$_{(2b)Allyl}$), 5.17 (d, J= 5.89 Hz, 4H, 2 × (α-CH$_2$)$_{Allyl}$), 4.78 (t, J = 6.34 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.91 (t, J = 6.80 Hz, 4H, 2 × CH$_2$-N), 2.26 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 143.87 (C$_{Ar}$-S), 142.64 (2 × CH$_{BImidazole}$), 134.93 (C$_{Ar}$-CH$_3$), 131.29 (2 × C$_{BImidazole}$), 130.93 (2 × C$_{BImidazole}$), 130.74 (2 × (CH)$_{Allyl}$, 129.63 (2 × CH$_{BImidazole}$), 126.85 (2 × CH$_{BImidazole}$), 126.74 (2 × CH$_{Ar}$), 126.42 (2 × CH$_{Ar}$), 124.35, 121.15, 117.95, 114.76 (q, J=322 Hz, CF$_3$), 120.60 (2 × (CH$_2$)$_{Allyl}$), 113.90 (2 × CH$_{BImidazole}$), 113.54 (2 × CH$_{BImidazole}$), 48.87 (2 × (α-CH$_2$)$_{Allyl}$), 46.08 (2 × CH$_2$-N), 44.72 (2 × CH$_2$-N$_{Ar}$), 20.98 (CH$_3$)$_{Ts}$; ^{19}F (336, MHz) δ ppm: −80.05 (CF$_3$); HRMS: m/z, [M^{+2}–H]−2NTF$_2^-$ calcd. for C$_{31}$H$_{34}$N$_5$O$_2$S^{3+} : 540.2433, found: 540.2426; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2^-$: 279.9173, found: 279.9138.

4.3.18 Synthesis of *N*,*N*-Bis[(3-(2-ethanolyl)-benzimidazol-1-iumyl)ethyl]-4-methyl-benzenesulphonamide bis(trifluoromethylsulphonyl)amide (8d)

This compound was prepared analogously to **7d** using *N*,*N*-bis[(3-(2-ethanolyl)-benzimidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide **6d** (0.71 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (0.72 g, 2.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 87% yield (0.97 g). Molecular Formula: C$_{33}$H$_{35}$F$_{12}$N$_7$O$_{12}$S$_5$; Mol. Wt.: 1,109.98; FTIR (cm^{-1}): 3,312 (O-H), 3,137, 3,027 (C-H)$_{Ar}$, 2,982 (C-H)$_{Aliph}$, 1,614, 1,596 (C=N)$_{Ar}$, 1,563, 1,485 (C=C)$_{Ar}$, 1,344, 1,221 (C-F), 1,330, 1,154 (O=S=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.72 (s, 2H, C-H$_{BImidazole}$), 8.07–8.01 (m, 4H, C-H$_{BImidazole}$), 7.73–7.67 (m, 4H, C-H$_{BImidazole}$), 7.33 (d, J = 8.31 Hz, 2H, C-H$_{Ar}$), 7.08 (d, J = 8.07 Hz, 2H, C-H$_{Ar}$), 5.20 (bs,

2H, 2 × O-H), 4.79 (t, *J*= 6.11 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 4.56 (t, *J*= 4.98 Hz, 4H, 2 × (α-CH$_2$)), 3.88 (t, *J* = 6.11 Hz, 4H, 2 × CH$_2$-N), 3.84 (t, *J*= 4.98 Hz, 4H, 2 × CH$_2$-OH), 2.27 (s, 3H, (CH$_3$)$_{Ts}$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 143.82 (C$_{Ar}$-S), 142.83 (2 × CH$_{BImidazole}$), 134.74 (C$_{Ar}$-CH$_3$), 131.21 (2 × C$_{BImidazole}$), 131.05 (2 × C$_{BImidazole}$), 129.92 (2 × CH$_{Ar}$), 129.57 (2 × CH$_{Ar}$), 126.67 (2 × CH$_{BImidazole}$), 126.48 (2 × CH$_{BImidazole}$), 124.33, 121.13, 117.93, 114.73 (q, *J*=322 Hz, CF$_3$), 113.95 (2 × CH$_{BImidazole}$), 113.37 (2 × CH$_{BImidazole}$), 58.62 (2 × C̲H$_2$-OH), 49.48 (2 × (α-CH$_2$)), 46.08 (2 × CH$_2$-N), 44.60 (2 × CH$_2$-N$_{Ar}$), 20.96 (CH$_3$)$_{Ts}$; ^{19}F (336, MHz) δ ppm: −80.20 (CF$_3$); HRMS: m/z, [M^{+2}–H]−2NTF$_2$$^{−}$ calcd. for C$_{29}$H$_{34}$N$_5$O$_4$S^{3+} : 548.2332, found: 548.2290; m/z, [NTF$_2$]$^{−}$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^{−}$: 279.9173, found: 279.9218.

4.3.19 Synthesis of *N,N*-Bis[(3-(2-*tert*-butoxy-2-oxoethyl)-benzimidazol-1-iumyl)-ethyl]-4-methylbenzenesulphonamide bis(trifluoromethylsulphonyl)amide (8f)

This compound was prepared analogously to **7d** using *N,N*-bis[(3-(2-*tert*-butoxy-2-oxoethyl)-benzimidazol-1-iumyl)ethyl]-4-methylbenzenesulphonamide bromide **6f** (0.85 g, 1.0 mmol) and Lithium bis-(trifluoro methanesulphonyl)imide LiNTf$_2$ (0.72 g, 2.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 97% yield (1.2 g). Molecular Formula: C$_{41}$H$_{47}$F$_{12}$N$_7$O$_{14}$S$_5$; Mol. Wt.: 1,250.16; FTIR (cm$^{−1}$): 3,065, (C-H)$_{Ar}$, 2,979 (C-H)$_{Aliph}$, 1,739 (C=O), 1,597 (C=N)$_{Ar}$, 1,564, 1,488 (C=C)$_{Ar}$, 1,364, 1,151 (O=S=O), 1,354, 1,222 (C-F), 1,088 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 9.76 (s, 2H, C-H$_{BImidazole}$), 8.05–8.00 (m, 4H, C-H$_{BImidazole}$), 7.72–7.67 (m, 4H, C-H$_{BImidazole}$), 7.39 (d, *J* = 8.07 Hz, 2H, C-H$_{Ar}$), 7.11 (d, *J* = 8.07 Hz, 2H, C-H$_{Ar}$), 5.51 (s, 4H, 2 × (α-CH$_2$)$_{TBE}$), 4.82 (t, *J*= 6.11 Hz, 4H, 2 × CH$_2$-N$_{Ar}$), 3.85 (t, *J*= 6.11 Hz, 4H, 2 × CH$_2$-N), 2.27 (s, 3H, (-CH$_3$)$_{Ts}$), 1.89 (s, 18H, 6 × (-CH$_3$)); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm : 167.97 (2 × C=O), 144.08 (C$_{Ar}$-S), 143.57 (2 × CH$_{BImidazole}$), 134.41 (C$_{Ar}$-CH$_3$), 131.50 (2 × C$_{BImidazole}$), 130.63 (2 × C$_{BImidazole}$), 129.73 (2 × CH$_{Ar}$), 127.04 (2 × CH$_{Ar}$), 126.93 (2 × CH$_{BImidazole}$), 126.73 (2 × CH$_{BImidazole}$), 124.24, 121.18, 117.95,

114.71 (q, J=322, CF$_3$), 113.99 (2 × CH$_{BImidazole}$), 113.54 (2 × CH$_{BImidazole}$), 83.57 (2 × C), 47.58 (2 × (α-CH$_2$)), 46.29 (2 × CH$_2$-N), 45.09 (2 × CH$_2$-N$_{Ar}$), 27.25 (6 × CH$_3$), 21.12 (CH$_3$)$_{Ts}$; ^{19}F (336, MHz) δ ppm: −80.09 (CF$_3$); HRMS: m/z, [M^{+2}–H]−2NTF$_2^-$ calcd. for C$_{37}$H$_{46}$N$_5$O$_6$S^{3+} : 688.3169, found: 688.3222; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2^-$: 279.9173, found: 279.9180.

4.3.20 Antibacterial Evaluation

Ten standard strains of Gram positive and negative bacteria were used to evaluate the antibacterial activities of the synthesized ILs compounds; **5a**–**f** and **6a**–**f**. Based on CLSI guidelines (Wikler, 2009), the activities were assessed in terms of minimum inhibitory concentrations (MICs) using microbroth dilution assays. The MIC's values are given in mg/mL and defined as a lowest concentration that inhibits the bacterial strains growth. Gram positive bacteria included: *Streptococcus pyogenes* ATCC19615, *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC6051, *Rhodococcus ruber* ATCC27863, *Enterococcus faecalis* ATCC 29212, *Staphylococcus epidermidis* ATCC12228, while Gram negative bacteria included: *Escherichia coli* ATCC10538, *Salmonella typhimurium* ATCC14028, *Pseudomonas aeruginosa* ATCC15442, *Acinetobacter calcoaceticus* ATCC 23055. These standards strains were obtained from the collection of Biosciences and Biotechnology School, Faculty of Science and Technology, University Kebangsaan, Malaysia.

Distilled water was used as negative control to dissolve all the tested ILs in concentrations range of 0.05− 0.5 mg/mL, while, commercial antibiotics amoxicillin and kanamycin were used as a positive control in the same range of concentrations. A loopful of bacterial cells from the nutrient agar plates of stock cultures was inoculated into 100 mL nutrient broth of 250 mL side arm Erlenmeyer flask. They were incubated at 37 °C for 16 h with vigorous shaking. After incubation, the culture was diluted with fresh media to produce an O.D 600 nm of 0.1. Fifty μL of standardized 18 h incubated

bacterial culture were introduced into test tubes containing 5 mL media, followed by addition various concentrations of the tested ILs. All assays were performed in triplicate

4.3.21 Thermal stability

Thermal stability in the term of decomposition temperatures of the synthesized halogen ILs was evaluated using thermogravimetric analyser (TGA Perkin Elmer TGA4000, with Pyris 9.1 software). For thermogravimetry measurements, an open alumina crucible of up to 10 mg weight samples were placed on a sample pan with 20 ml·min^{-1} flow-rate of high pure nitrogen at ambient temperature. Consequently, the samples were heated from 35 to 900 °C, at heating rate of 10 °C min^{-1} and the weight change was recorded as a function of the heating temperature. The decomposition temperatures are stated in terms of T_{start} (the temperature at which the decomposition of the sample starts), $T_{10\%}$ and $T_{50\%}$ (the temperatures at which a mass loss of 10% and 50%, respectively, is reached), T_{peak} (the maximum temperature derivative of the weight change with respect to time), as well as T_{onset} (the intersection of the zero mass loss baseline and the tangent line through T_{peak}).

4.4 CONCLUSIONS

Novel sets of halogen and NTF$_2$ di-imidazolium and di-benzimidazolium ILs containing a high rigid spacer incorporated into benzenesulphonamide moiety and various active side substituents were successfully prepared. The structures of these di-cationic ILs were confirmed by classical FTIR, NMR, and HRMS techniques. Metathesis of halogen anion to NTf$_2$ turned all the ILs to clear liquids at room temperature in excellent yield and purity. Both imidazolium and benzimidazolium series of halogen anions were evaluated for thermal stability as well as *in vitro* antibacterial activities against ten strains of bacteria. The miscibility of the prepared ILs in both water and common organic solvents are studied as well. ILs with acetonitrile substituents (*i.e.* **5c** and **6c**) on imidazolium rings displayed the highest bioactivity and

onset decomposition temperature among the studied dicationic ILs. However, most of these ILs demonstrated significant activities against both Gram-positive and Gram-negative bacteria compared to commercial antibiotics; amoxicillin and kanamycin beside of their high thermal stability. Generally, ILs bearing imidazolium dications exhibited the higher results of antibacterial activity and thermal stability as compared to those with benzimidazolium dicationic. Surface properties including critical micelle concentration CMC, surface tension γ_{cmc}, Krafft temperature and Cloud point as well as more physical properties of the synthesized geminal dicationic ILs (*e.g.*, viscosity and fluorescence) will be reported in due course.

CHAPTER 5: TRIS-IMIDAZOLIUM AND BENZIMIDAZOLIUM IONIC LIQUIDS: A NEW CLASS OF BIODEGRADABLE SURFACTANTS

Nassir N. Al-Mohammed, Rusnah Syahila Duali Hussen, Yatimah Alias and Zanariah Abdullah, *RSC Advances*, manuscript published December-2-2014
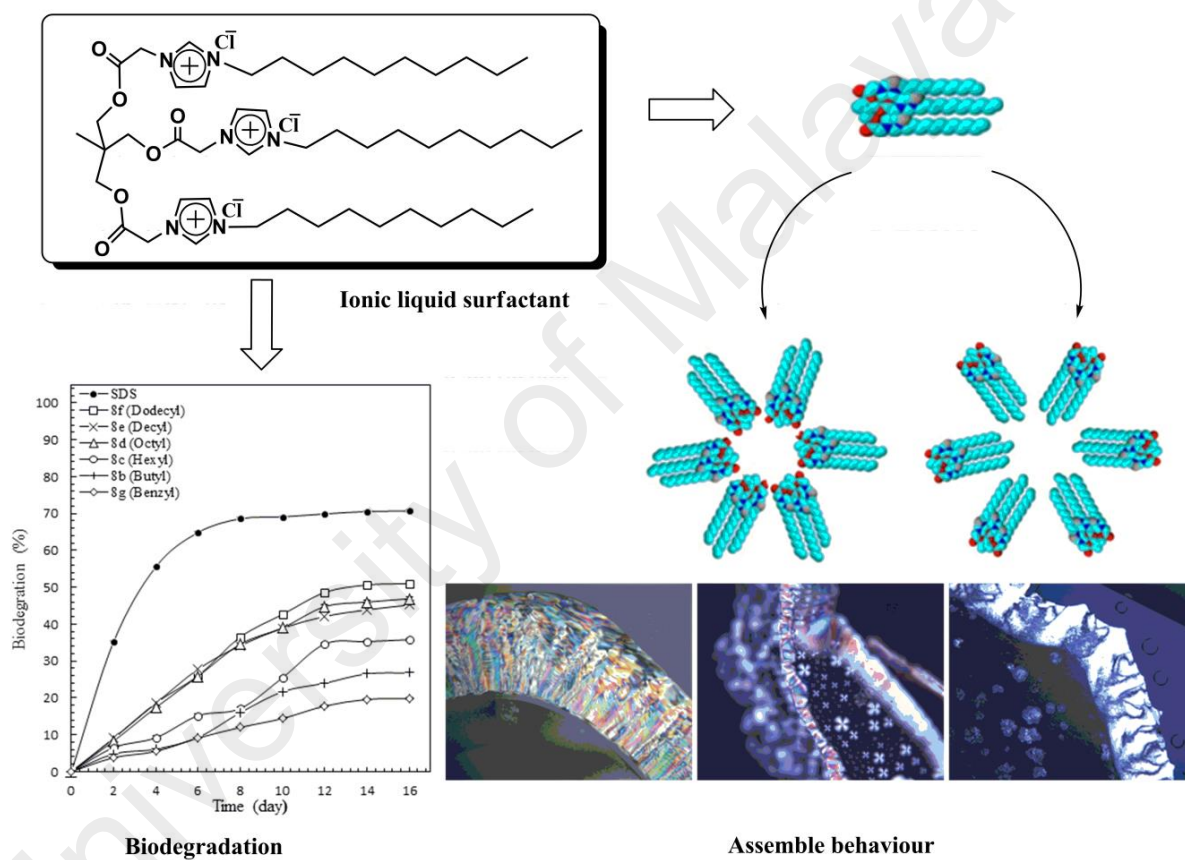
Factors that improved the biodegradation of surfactants have successfully used to prepare higher ordered biodegradable tris-imidazolium and benzimidazolium ILs.

5.1 INTRODUCTION

Ionic liquids (ILs) are organic salts that melt below 100 °C and consist of bulky organic cations associated with either organic or inorganic anions (Seddon, 2003; Wilkes, 2002). Typically, the most common organic cations are either imidazolium, pyridinium, or pyrrolidinium, with alkyl chain substituents (Davis, 2004; Wasserscheid & Welton, 2007) while the anions include halogen, $[AlCl_4]^-$, $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$, $[(CF_3SO_2)_2N]^-$, or $[n\text{-}C_8H_{17}OSO_3]^-$ (Wasserscheid, Hal, & Bosmann, 2002). ILs have increasingly become attractive as ''green'' solvents (or environmental friendly) for a wide range of applications due to their low vapour pressure with recycling and catalytic ability (Gordon, 2001; Li *et al.*, 2013; Munshi, Biradar, Gade, Rane, & Kelkar, 2014; Rooney & Seddon, 2001; Sheldon, 2001; Sheldon, 2005; Welton, 1999).

In principle, the physicochemical properties of IL solvents can be tailored for a given application by varying the cationic (or anionic) components. Thus, their properties including melting point, solubility, viscosity, thermal stability and hydrophobicity can be adjusted to suit a variety of wide applications. Some ILs also have surfactant behaviour; therefore, their assemblies can be tuneable by adjusting the solvent composition. Application of ILs as a solvent coupled with their liquid crystalline behaviour could be an advantage in anisotropic ion-conductors, templating and electrolytes in dye-sensitizer solar cells (Axenov & Laschat, 2011; Chi, Jeon, Kim, Kim, & Kim, 2013).

Through thorough studies against a wide range of organisms, the popular used ILs are proven as toxic in nature (Santos, Ribeiro, Alviano, & Coelho, 2014; Zhao, Liao, *et al.*, 2007) where the both cationic and anionic components have influence on the toxicity (Hajfarajollah, Mokhtarani, Sharifi, Mirzaei, & Afaghi, 2014; Petkovic *et al.*, 2010). Moreover, ILs that consist of a substituted cation with long linear hydrocarbon side chains ≥ 8 carbon atoms presented varying toxicity levels (Stolte *et al.*, 2007;

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Swatloski *et al.*, 2004). The positive head group of the cation plays essential role in IL toxicity (Garcia-Lorenzo *et al.*, 2008) where the longer side chains have further biological serious influence on living cells (Morrissey *et al.*, 2009; Pernak & Chwała, 2003). At the same time, ILs demonstrated various levels of toxicity magnitude comparing to conventional organic solvents: acetone, acetonitrile, methanol, dichloro-methane and methyl *t*-butyl ether (Ranke *et al.*, 2004; Wells & Coombe, 2006). First study related ILs toxic nature contributed by Jastorff *et al.* (2003) when reported theoretical multidimensional analysis of two ILs. They proposed environmental risk assessment of 1-butyl-3-methylimidazolium tetrafluoroborate and 1-decyl-3-methyl-imidazolium tetrafluoroborate ILs with acetone as an organic solvent reference. Five ecotoxicological indicators were considered in this multidimensional analysis including: release, spatiotemporal range, bioaccumulation, biological activity and uncertainty. Further, the first comprehensive biological study (Ranke *et al.*, 2004), included the effects of different *n*-alkyl chains for methyl- and ethyl-imidazolium ILs incorporated with variety of anions. The study revealed that ILs is toxicity increasing due to elongation in both alkyl chains length of imidazolium ring. Obviously, ILs may have greater potential to bioaccumulate (persist in the environment) and vice versa when not passing biodegradation tests. Further studies of biodegradation, mineralization and bioaccumulation are necessary to estimate the toxic hazards of ILs or their persisting in the environment. Although different studies on ILs, including toxicity, ecotoxicity and biodegradation have been reported in the literature (Docherty & Kulpa, 2005; Jastorff *et al.*, 2005; Kulacki & Lamberti, 2008; Latala, Nedzi, & Stepnowski, 2010; Matzke *et al.*, 2007; Zhao, Liao*, et al.*, 2007), biodegradation data are still seldom. Wells and Coombe (2006) screened the biodegradation of ammonium, imidazolium, phosphonium and pyridinium ILs using Biochemical Oxygen Demand measurements in five days (BOD$_5$). Most of the investigated alkyl side chain ILs showed biodegradation resistant.

The first biodegradable compounds presented by Boethling (Boethling, 1994; Boethling, 1996) when highlighted the importance of biodegradable chemicals through biodegradable surfactants design for linear alkylbenzenesulfonates and dialkyl quaternaries. Furthermore, Boethling presented readily biodegradable compounds when introduced the long linear hydrocarbon side chain into an ester group. Generally, the biodegradable surfactants have been developed based on: (i) the existence of potential sites of esters as an enzymatic hydrolysis, (ii) the introduction of oxygen in the form of hydroxyl, aldehyde or carboxylic acid groups, in addition to (iii) the existence of unsubstituted long linear alkyl chains or phenyl rings, which represent potential sites for attack by oxygenases (Boethling, 1994; Boethling, 1996; Howard *et al.*, 1991). Hydrolysable bond (esters or amides) as functional groups introduced into the ILs cation side chain were required to synthesize early biodegradable ILs. The same principles were followed by Gathergood and co-workers (Gathergood *et al.*, 2004; Gathergood & Scammells, 2002), when evaluated the biodegradation for series of dialkylimidazolium ILs with ester or amide containing side chains by using the closed bottle tests (OECD 301 B and D). Compounds with biodegradation levels of 60 % or higher are considered to be ''readily biodegradable'' (Coleman & Gathergood, 2010; Gathergood *et al.*, 2006).

The design of potential biodegradable ILs was affected by structure of the components that include most ILs: the cation core, cation side chain(s), and the anion. Imidazole such as the common amino acid; histidine is known to be degraded by microorganisms (Wadud, Onodera, & Or-Rashid, 2001). Further, imidazolium core has close structural relationship with surfactant like quaternary ammonium compounds (Coleman & Gathergood, 2010); therefore, imidazolium moieties were selected as the cation core. Thus, the factors that improved the biodegradation of surfactants could be applicable to design the ILs cation able to self-assemble with or without the presence of

a solvent. From the surfactant point of view, rod-like molecules such as single-chain imidazole derivatives are generating nematic (N) and bilayer smectic A (SmA) phases (Cheng *et al.*, 2010; Plechkova & Seddon, 2008) while triple-tails compounds have the tendency to form wedge-shape molecules. They have the affinity to form higher ordered molecular arrangements such as columnar (col) or cubic (cub) phases (Ichikawa *et al.*, 2012; Sander *et al.*, 2011). Consequently, higher ordered phases are good candidates for application as anisotropic ion conductors (Axenov & Laschat, 2011).

Although many researchers (Gathergood & Scammells, 2002; Handy, 2003; Neumann *et al.*, 2014; Steudte *et al.*, 2014; Stolte *et al.*, 2008; Tao, He, Sun, & Kou, 2005) have studied degradable ILs, none have approached tri-cationic ILs in the literature up to authors' knowledge. The current study concentrates on the synthesis of novel tris-imidazolium and tris-benzimidazolium degradable ILs surfactants, containing incorporated alkyl or phenyl side chains with tri-ester groups in the same molecule. Towards degradable halogen-IL surfactants with higher ordered molecular arrangements phases, a unique evaluation of biodegradation, phase behaviour and their interaction with water are investigated. Broad practical applications of industrial and medical applications are highly expected. The effects of anions on phase behaviour and biodegradation are beyond the scope of this study.

5.2 RESULTS AND DISCUSSION

5.2.1 Synthesis

ILs syntheses described in current study are based on a simple approach which was modified to prepare tris-imidazolium and tris-benzimidazolium ILs from readily available starting materials in high yield. This process involved alkylation of alkyl-imidazole and alkyl-benzimidazole with appropriate tri-ester halide that was synthesized by simple esterification of 1,1,1-tris (hydroxymethyl)ethane in net chloroacetyl chloride. Furthermore, the halides in the alpha position to carbonyl compound reflect excellent

starting materials for high purity and excellent yield of ILs. The synthesis of different

length chain of alkyl imidazoles and benzimidazoles was beneficial to obtain plenty of

ILs derivatives. Thus, the treatment of imidazole or benzimidazole with alkyl halides

under basic conditions affords alkyl imidazoles (and benzimidazole) in optimum yield.

Alkylation of the obtained alkyl imidazoles and benzimidazoles with active tri-ester

halide in acetonitrile at 45–55 °C produced the quantitative yield of certain ILs as

shown in Figure 5.1.

R		$X^- = Cl^-$	$X^- = NTf_2^-$
a	-CH$_3$	8a	10a
b	n-C$_4$H$_9$	8b, 9b	10b, 11b
c	n-C$_6$H$_{13}$	8c, 9c	10c
d	n-C$_8$H$_{17}$	8d, 9d	11d
e	n-C$_{10}$H$_{21}$	8e, 9e	10e, 11e
f	n-C$_{12}$H$_{25}$	8f, 9f	11f
g	-CH$_2$Ph	8g, 9g	10g, 11g
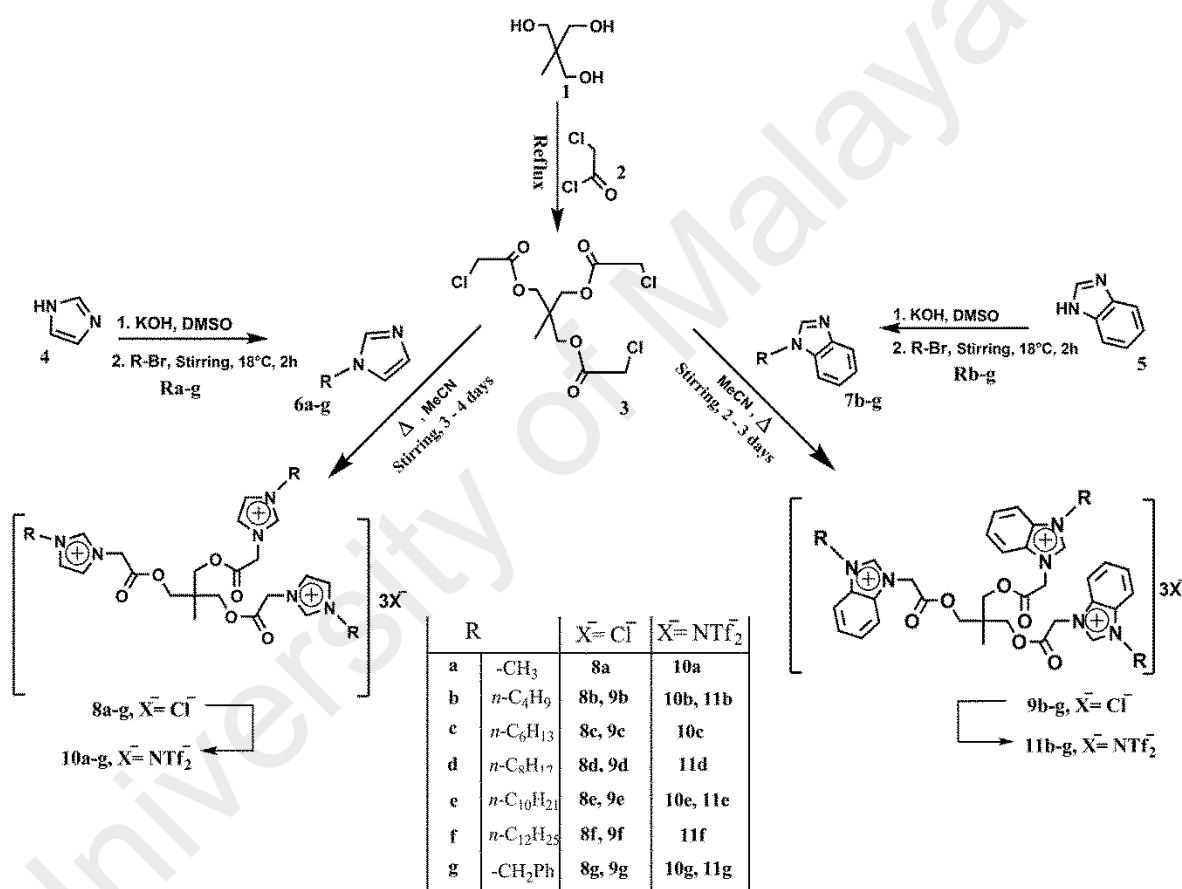
Figure 5.1: Synthesis of tris-imidazolium and tris-benzimidazolium ILs

All the chloride ILs prepared in current work are semi-solid to syrup at room

temperature which have been set as reference point to determine their classification as

ILs (Seddon, 2003). Metathesis of halogen anion to NTf$_2^-$ produced clear liquids at

room temperature and clean samples were isolated after a simple workup. The process

included mixing an aqueous solution of chloride salt with LiNTf$_2$. The hydrophobic IL

phase was then separated by simple extraction with ethyl acetate to produce pure ILs

after organic layer evaporation under the reduced pressure. Table 5.1 summarizes the synthetic details of the prepared ILs.

Table 5.1: Structural and synthetic details of tris-imidazolium and tris-benzimidazolium ILs

IL	Cations	Alkyl chains	Counter ions	Status[c]	M.wt.	Yield (%)
8a	Im[a]	CH$_3$	Cl	Semi-solid	595.90	97
8b	Im[a]	n-C$_4$H$_9$	Cl	Syrup	722.14	98
8c	Im[a]	n-C$_6$H$_{13}$	Cl	Syrup	806.30	98
8d	Im[a]	n-C$_8$H$_{17}$	Cl	Syrup	890.46	97
8e	Im[a]	n-C$_{10}$H$_{21}$	Cl	Syrup	974.62	99
8f	Im[a]	n-C$_{12}$H$_{25}$	Cl	Syrup	1058.78	99
8g	Im[a]	-CH$_2$-Ph	Cl	Semi-solid	824.19	91
9b	BIm[b]	n-C$_4$H$_9$	Cl	Syrup	872.32	97
9c	BIm[b]	n-C$_6$H$_{13}$	Cl	Syrup	956.48	99
9d	BIm[b]	n-C$_8$H$_{17}$	Cl	Syrup	1040.64	98
9e	BIm[b]	n-C$_{10}$H$_{21}$	Cl	Syrup	1124.80	99
9f	BIm[b]	n-C$_{12}$H$_{25}$	Cl	Syrup	1208.96	99
9g	BIm[b]	-CH$_2$-Ph	Cl	Semi-solid	974.37	96
10a	Im[a]	-CH$_3$	NTf$_2$	liquid	1329.98	81
10b	Im[a]	n-C$_4$H$_9$	NTf$_2$	liquid	1456.22	84
10c	Im[a]	n-C$_6$H$_{13}$	NTf$_2$	liquid	1540.38	85
10e	Im[a]	n-C$_{10}$H$_{21}$	NTf$_2$	liquid	1708.70	94
10g	Im[a]	-CH$_2$-Ph	NTf$_2$	liquid	1558.27	91
11b	BIm[b]	n-C$_4$H$_9$	NTf$_2$	liquid	1606.39	84
11d	BIm[b]	n-C$_8$H$_{17}$	NTf$_2$	liquid	1774.71	90
11e	BIm[b]	n-C$_{10}$H$_{21}$	NTf$_2$	liquid	1858.88	90
11f	BIm[b]	n-C$_{12}$H$_{25}$	NTf$_2$	liquid	1943.04	96
11g	BIm[b]	-CH$_2$-Ph	NTf$_2$	liquid	1708.45	96

[a] Imidazolium
[b] Benzimidazolium
[c] at room temperature

5.2.2 Liquid crystalline behaviour

Optical polarizing microscope equipped with heating stage was used to investigate liquid crystalline properties of compounds **8b-f** and **9b-f** thermotropically and lyotropically as highlighted in the experimental section. In absence of solvents, compounds **8b**, **8c**, **8d** and **9b**, **9c**, **9d** appeared to be viscous fluids at room temperature with no birefringence, while compounds with ≥ C10 carbons chains length showed birefringent at room temperature. Tris-imidazolium series showed birefringent property with clearing points of 116 °C and 172 °C for compounds **8e** and **8f**, respectively. Both compounds expected to form smectic A phases (oily streaks) based on the textures

shown in Figure 5.2. While tris-benzimidazolium compound series showed relatively lower clearing point *i.e.* 37 °C for **9e** and 50 °C for **9f**. The benzanelation of the imidazole reduced the clearing point significantly and increased the molecules area of nonpolar domain; thus, the chains packed in a wedge-shaped molecule which favours the formation of columnar phase (Figure 5.3). Precisely, ascending and descending trends was observed in clearing points of tris-imidazolium and benzimidazolium ILs, respectively, as a function of chains length increasing illustrated in Table 5.2. Clearing point is the transition temperature between liquid crystalline phase (mesophase) and isotropic liquid, whereas the liquid crystal phase is completely converted to an isotropic liquid above the clearing point (Axenov & Laschat, 2011; Goodby *et al.*, 2008).
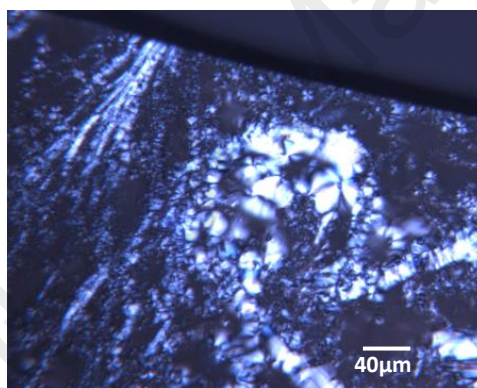
Figure 5.2: The oily streaks texture observed under polarized microscope for compound **8f** at 25°C (50×).
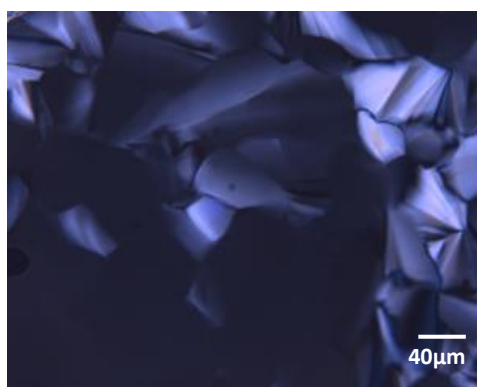
Figure 5.3: The columnar texture observed under polarized microscope for compound **9e** at 25°C (50×).

Lyotropic investigation was performed using contact penetration scans method where the samples are sandwiched between two slides with or without adding solvent at the

slide edge. The solvent diffused through the sample by capillary force then the liquid crystalline phase was formed when the solvent penetrated the sample with different concentration gradient. Water as polar solvent and 1-undecanol as nonpolar were used to investigate the polymorphism in different systems. In water penetration study, compounds **8b**, **8c**, **9b**, **9c**, and **9d** are very soluble; therefore, the formation of micellar, L_1, solution was expected, while for compounds **8d**, **8e** and **8f**, a normal hexagonal phase, H_1, was observed with slow dissolving into L_1 phase. In contrast, tris-benzimidazolium compounds series were less soluble and exhibited a cubic phase. The penetration profile of compound **8f** at room temperature is shown in Figure 5.4 and the image for **9e** in contact with water is shown in Figure 5.5.
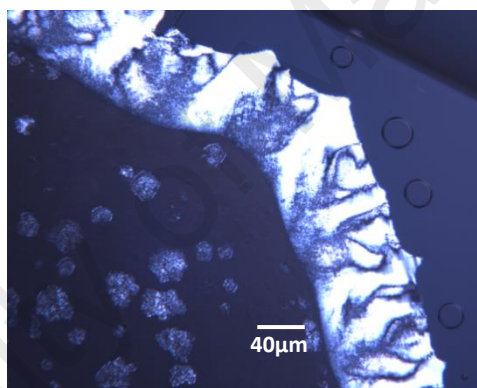
Figure 5.4: Water penetration scans observed under polarized microscope for compound **8f** at 25 °C (50×).
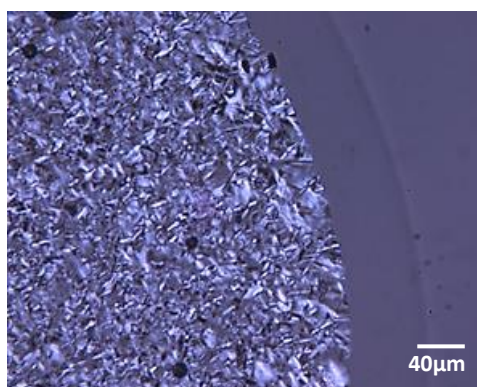
Figure 5.5: Water penetration scans observed under polarized microscope for compound **9e** at 25 °C (20×).

The behaviour of tris-imidazolium series in contact with nonpolar solvent showed that longer chain compound *i.e.* **8f** is very soluble to form an inverted micellar solution,

L$_2$. Further, additional liquid crystalline phases were observed for **8b**, **8c**, **8d** and **8e** besides the L$_2$. *E.g.* inverted hexagonal (H$_2$), Maltese crosses with H$_2$ and finally lamellar phases with H$_2$ for **8b**, **8c** and **8d** ILs, respectively, as depicted in Figure 5.6.
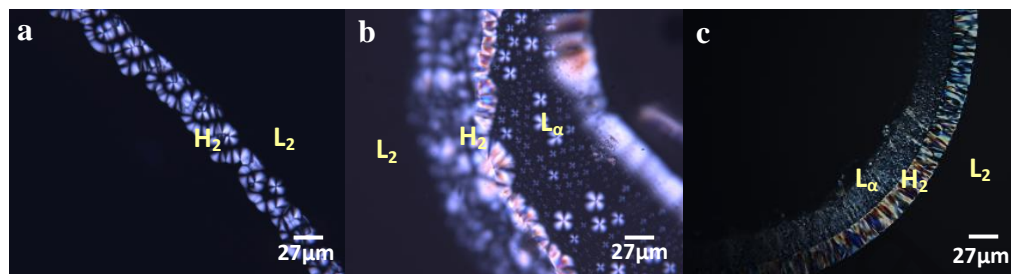
Figure 5.6: 1-Undecanol penetration scans for compounds (a) **8b** (b) **8c** (c) **8d** at 25 °C (50×).

Compounds **9b** and **9c** did not show any liquid crystal phase in contact with 1-undecanol, while compound **9d** exhibited inverted hexagonal and inverted cubic phases. Generally, longer chains length of tris-benzimidazolium compounds such as **9e** and **9f** displayed H$_2$ and lamellar phases as presented in Figure 5.7.
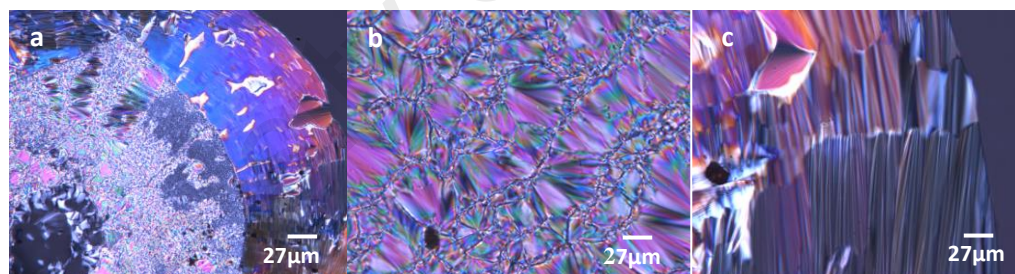
Figure 5.7: 1-Undecanol penetration scans at 25 °C for compound **9e** (a) overall scan penetration study taken at (10×) magnification, (b) zoom for the lamellar phase (50×), and (c) the outer penetration displays H$_2$ (50×).

For this type of mesogen in both tris-imidazolium and benzimidazolium ILs, compounds starting with 10 carbon alkyl chains showed a birefringent behaviour while shorter than 10 are most likely not flexible enough to align unisotropically. In present liquid crystal phase, the molecules are still ordered in some direction with flows like a liquid. According to literature, the same trend was noticed for 2-tridecylpyridine chloride (Sudholter, Engberts, & De Jeu, 1982) which melts at 52 °C and clears at 109

°C. Moreover, the materials based on IL can self-assemble into a liquid crystal phase by solvent addition; for example, triethylammoniumdodecyloxycyanobiphenyl bromide showed lamellar phase in contact with water (Attard, Fuller, Howell, & Tiddy, 2000). Thus, the phase behaviour of ILs can be produced in pure state (spontaneously) and during their interaction with polar and nonpolar solvents.

Prediction and cartoon molecular alignment of IL material in the liquid crystalline phase is illustrated in Figure 5.8 where the micro-phase separation within the material is the driving force for its assembly. At the molecular level, all alkyl chains are aligned in parallel as depicted in Figure 5.8 (a) for compound **8e**, while, at lower concentration of solvent, the material is preferably arranged in a smectic A or lamellar phase as illustrated in Figure 5.8 (b). Further, in contacting with solvent, the molecules tend to reassemble depending on the nature of solvents. Where in water, the chains arranged near each other with the polar part domain contacted to water as demonstrated in Figure 5.8 (c). The reverse arrangement occurred in contact with 1-undecanol, where several discs assembled together to form hexagonal phase as shown in Figure 5.8 (d). Phase behaviour summarization results of synthesized tris-imidazolium and bezimidazolium ILs are illustrated in Table 5.2.

(a)

(b)   (c)   (d)
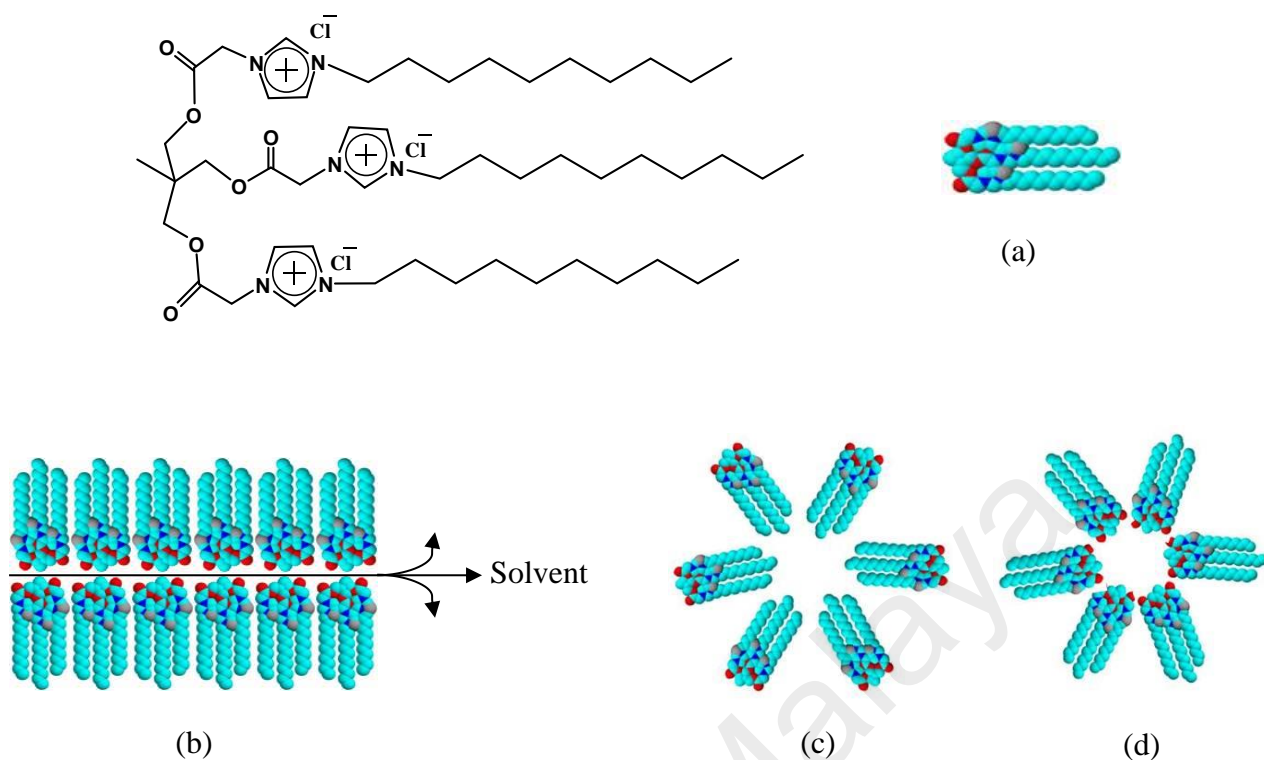
Figure 5.8: Assembly illustration of (a) single molecule, (b) molecules arrangement in lamellar phase, (c) molecules arrangement in normal hexagonal, H_1 and (d) molecules arrangement in inverted hexagonal, H_2.

Table 5.2: Phase behaviours of the synthesized tris-imidazolium and bezimidazolium ILs as a function of alkyl chain length.

IL	Number of carbon atoms in side chains	Clearing point (°C)	Phase behaviour		
			In pure[b]	In water[c]	In 1-undecanol[d]
8b	4	ND[a]	Non-birefringent	Soluble	H_2
8c	6	ND[a]	Non-birefringent	Soluble	H_2, L_α
8d	8	ND[a]	Non-birefringent	I_1, H_1, V_1	H_2
8e	10	116	Smectic A	H_1	H_2
8f	12	172	Smectic A	H_1	H_2
9b	4	107	Non-birefringent	Soluble	I_2
9c	6	103	Non-birefringent	Soluble	I_2
9d	8	90	Non-birefringent	Soluble	H_2
9e	10	37	Columnar	I_1	H_2
9f	12	50	Columnar	H_1	H_2

[a] not detected

[b] is absence of solvent

[c] is contact with water

[d] is contact with 1-undecanol

5.2.3 Air-water interface behaviour

Results of surface properties including critical micelle concentration CMC, and surface tension γ_{cmc} as well as Krafft temperature, T_K, are presented in Table 5.3. The

values of T_K for all ILs solutions are below 10 °C. The surface tension measurements were recorded at 25 °C. The synthesized IL materials showed very low Krafft points indicating their solubility below room temperature and IL CMC results can be measured at room temperature. As expected, CMC values of ILs (Table 5.3) decreased with increasing chain length, where, compounds with 4 carbons at chain length are very soluble in water and the CMC values are expected to be higher than 150 mM based on a preliminary investigation. Essentially, the compounds showed common trend for single chain non-ionic surfactant such as alkyl maltosides (B. J. Boyd, C. J. Drummond, I. Krodkiewska, & Grieser, 2000). It is a decreasing by factor 10 upon addition of two methylene groups except the compounds with 10 and 12 carbon atoms in side chains for both tris imidazolium and benzimidazolium ILs. The deviation from the trend may be attributed to multiple charges at high dilution of the IL, which destabilize the micellar assembly. Thus, the synthesized ILs materials lowered the water surface tension to 28-31 mN m^{-1}. Moreover, the hydrophobicity of ILs materials had very minor influence on the molecules packing at air/water interface. However, this only applied to the tris-imidazolium series. For the molecular shape a non-parallel alignment of the alkyl chains is assumed, figuring the shape of a tripod.

Table 5.3: CMC, surface properties and Krafft temperature of ILs/water systems at 25 °C

IL	Carbon atoms in side-chains	Cmc (mM)	γ_{cmc} (mN/m)	T_K (°C)
8b	4	—	—	—
8c	6	62.0	29	<10
8d	8	6.5	28	<10
8e	10	1.3	28	<10
8f	12	0.89	29	<10
8g	Benzyl	—	—	—
9b	4	—	—	—
9c	6	40.8	29	<10
9d	8	3.8	31	<10
9e	10	0.9	30	<10
9f	12	0.3	31	<10
9g	Benzyl	—	—	—

5.2.4 Biodegradation results

'Closed bottle' OECD 301D test was used to evaluate the biodegradability of synthesized ILs as highlighted in the experimental section. ILs with only imidazolium cations revealed higher degradation than those based on benzimidazolium moieties as shown in Figures 5.8 and 5.9. Further, the biodegradation was improved to highest percent of 51% in **8f** (dodecyl side chain), due to alkyl side chain length increment (Docherty *et al.*, 2007) as illustrated in Figure 5.9. The presence of fused aromatic rings increased the stability of the ILs towards microbial degradation, therefore, changing the cationic part to benzimidazolium compound **9f** (dodecyl side chain) has reduced the IL degradation to 45% as shown in Figure 5.10.

Moreover, the tri-ester linkages improved the biodegradation progression of the synthesized ILs; and upon concordance, it was agreed that microbial enzymatic hydrolysis of the ester bonds could be the possible initiation stage in degradation enhancement. As a result, separation of imidazolium-alkyl chain fragment and the corresponding primary alcohol that is considered as readily metabolized *via* fatty acid β-oxidation was achieved (Gathergood *et al.*, 2004; Scott & Jones, 2000; Zhao, Liao*, et al.*, 2007). The ILs biodegradation was promoted due to reasonable solubility for both of the produced fragments in water. Similar trend in degradation percentage has previously reported in literature (Gathergood *et al.*, 2004) for ILs with mono-imidazolium cation containing ester groups.
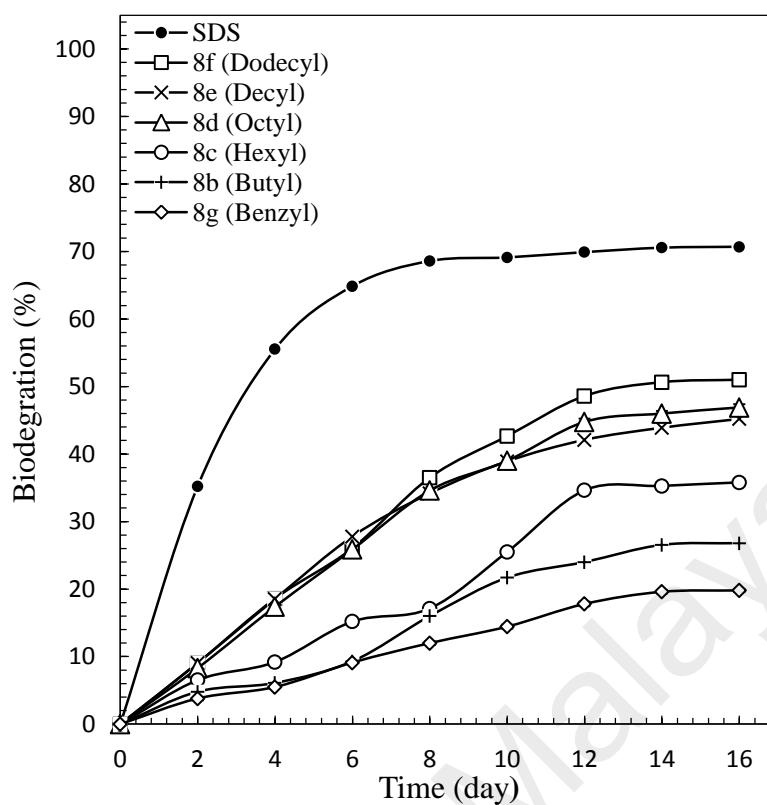
Figure 5.9: Biodegradation curves of tris-imidazolium ILs series using closed-bottle test.
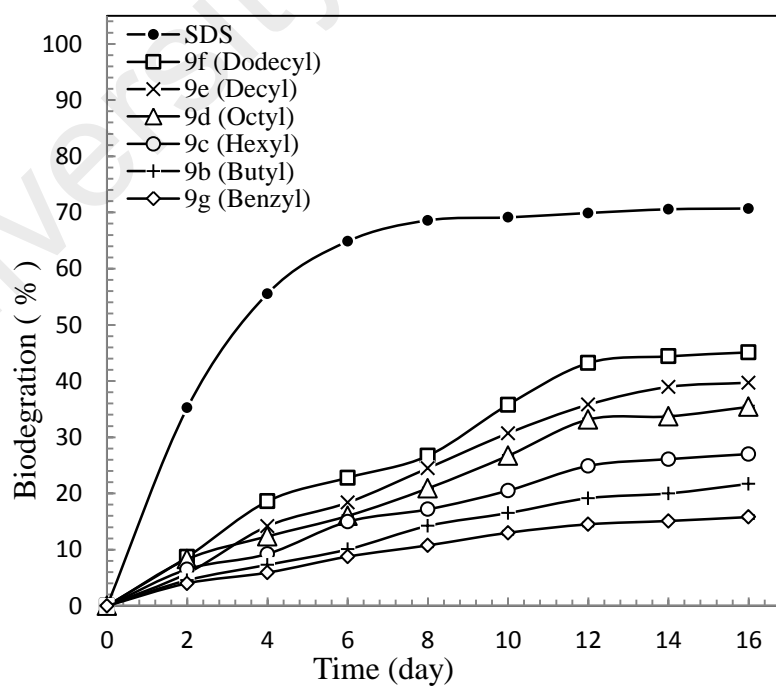
Figure 5.10: Biodegradation curves of tris-benzimidazolium ILs series using closed-bottle test.

For the purpose of starting and ending the test identification based on standard SDS samples results (Coleman & Gathergood, 2010; Sigua, Adjei, & Rechcigl, 2005) and current ILs biodegradation curves, 16 days test duration was considered due to attain a plateau from the last three measurements of these curves as shown in Figures 5.9 and 5.10. Moreover, obvious difference in biodegradation values was noticed in 10 days comparing to 16 days of the test duration as shown in Figures 5.11 and 5.12.

Furthermore, the presence of aliphatic alkyl side chain altered the hydrophobicity of mono-cationic ILs and subsequently enhanced their biodegradation (Docherty *et al.*, 2007). In comparison to mono-cationic ILs (Garcia *et al.*, 2005; Gathergood *et al.*, 2004; Ventura *et al.*, 2013), current tris-cationic ILs showed a higher degradation percentage within shorter test duration in the presence of long linear alkyl side chains. Moreover, changing the side chains from aliphatic groups (butyl- dodecyl) to aromatic chains (benzyl) demonstrated a significant decreasing in degradation; 20 % and 16% in both **8g** and **9g**, respectively, as shown in Figures 5.11 and 5.12. The summarized biodegradation results of synthesized tris-imidazolium and bezimidazolium ILs are illustrated in Table 5.4.

Table 5.4: Biodegradation results of synthesized tris-imidazolium and bezimidazolium ILs as a function of alkyl chains length.

IL	Carbon atoms in side-chains	Biodegradation (%)	
		10 day	*16 day*
8b	4	22	27
8c	6	25.5	36
8d	8	39	47
8e	10	39	45
8f	12	43	51
8g	Benzyl	14.5	20
9b	4	16.5	22
9c	6	20.5	27
9d	8	27	35.5
9e	10	31	40
9f	12	36	45
9g	Benzyl	13	16
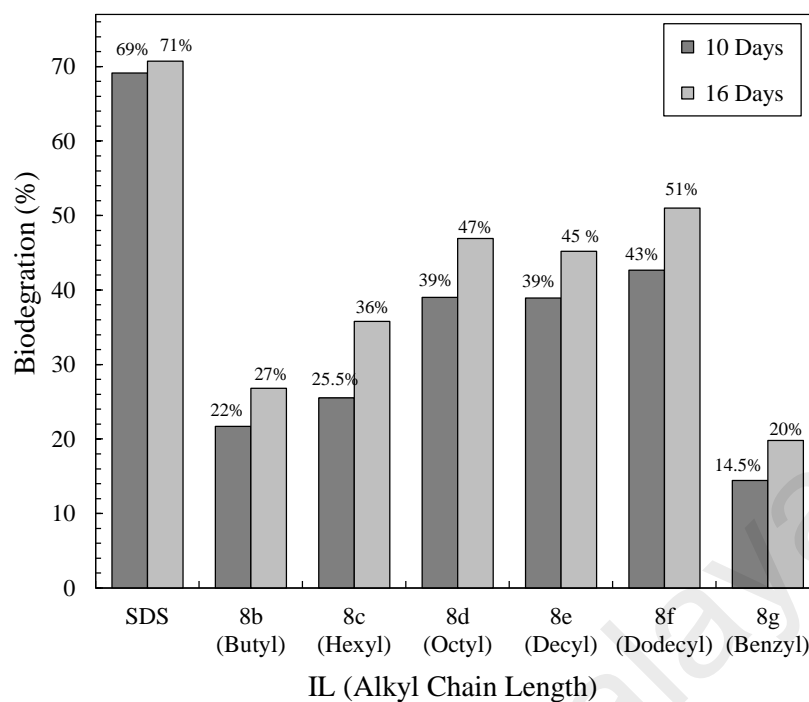
Figure 5.11: Biodegradation of tris-imidazolium ILs series as a function of aliphatic or aromatic side chains on 10 and 16 days.
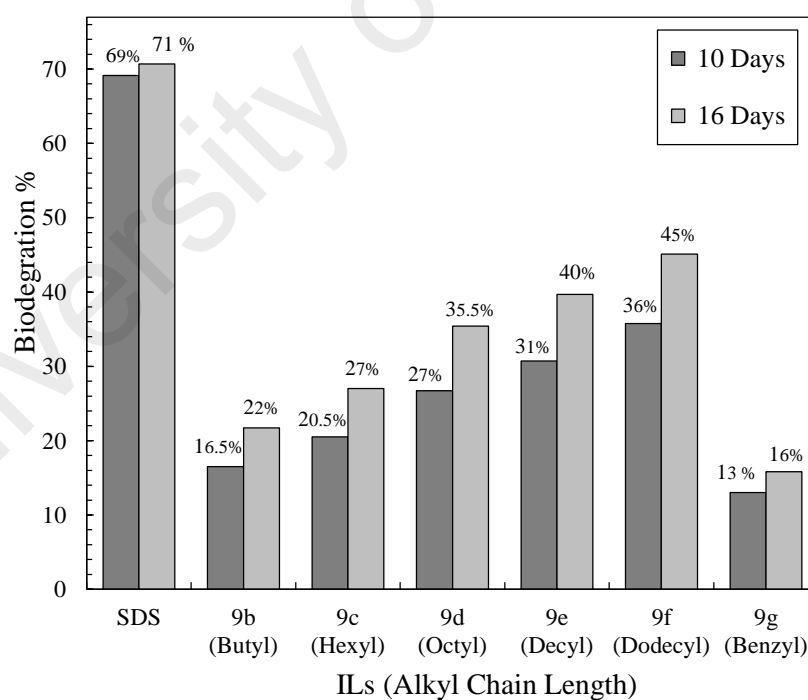
Figure 5.12: Biodegradation of tris-benzimidazolium ILs series as a function of aliphatic or aromatic side chains on 10 and 16 days.

Generally, the tested ILs displayed significant levels of biodegradation, where ILs (**8d**, **8e**, **8f** and **9f**) showed distinctive biodegradability values of 47%, 45%, 51%, and

45%, respectively, after 16 days period from test evaluation. The results indicated that these ILs are on the border of 60% pass level of readily biodegradation (Docherty *et al.*, 2007; Gathergood & Scammells, 2002; Gathergood *et al.*, 2006).

5.3. CONCLUSIONS

Tris-imidazolium and tris-benzimidazolium ILs containing alkyl or phenyl side chains with tri-ester groups are generally found as semi-solid to syrup at room temperature. Metathesis of chloride anion to NTf_2 was tuned it to liquids in excellent yield and purity. In absence of solvent, only compounds with ≥ 10 carbon atoms at their hydrocarbon chains showed assembly behaviour. The compounds containing 8 carbon atoms are still possible to assemble by addition of solvents either polar or nonpolar. These ILs surfactants are useful in wide temperature range with Krafft temperature lower than 10 °C and effectively reduce the water surface tension to 29 mN m^{-1}. The imidazolium ILs resulted significant increasing in phase behaviour properties and biodegradation compared to benzimidazolium ILs. Generally, ILs bearing imidazolium cations exhibit higher percentages of degradation as compared to those with benzimidazolium.

The factors that improved the biodegradation of surfactants have successfully been used to develop the biodegradation and self-assemble behaviour of the synthesized tri-cationic ILs. Further, comparing to mono-cationic ILs, these developed properties of synthesized tris-imidazolium and benzimidazolium ILs are highly enhanced by increasing the ILs hydrophobicity. Precisely, ILs incorporating the long linear alkyl (*i.e.* octyl, decyl, dodecyl) in the side chains presented on the border of the 60% pass level of readily biodegradation results with capability to self-assemble spontaneously or in the presence of a solvent.

The resistance to aerobic biodegradation is generally increased for compounds with halogens (chloride) as a counter ion (Coleman & Gathergood, 2010). Therefore, a more

detailed study of counter-ion effect on biodegradation is in progress towards readily biodegradable for these tris-imidazolium and benzimidazolium ILs. Antibacterial evolution for current ILs will be reported in future work. Furthermore, the determination of the physical properties of the synthesized ILs (*e.g.* solubility, thermal stability, cyclic voltammetry and fluorescence) will be reported in due course.

5.4 EXPERIMENTAL

5.4.1 General

1-Methylimidazole (99%) and 1-butylimidazol (98%) were purchased from Aldrich and distilled before usage to remove the detrimental impurities. 1-hexyl- imidazole, 1-octylimidazole, 1-decylimidazole, 1-dodecylimidazole, 1-benzylimidazole, 1-butylbenz-imidazole, 1-hexylbenzimidazole, 1-octylbenzimidazole, 1-decylbenzimidazole, 1-dode-cylbenzimidazole, and 1-benzylbenzimidazole were prepared as described below. 1-bro-mohexane, 1-bromooctane, 1-bromodecane, 1-bromododecane and benzyl bromide were obtained from commercial sources and used without further purification. All ILs were kept in fridge (5 °C) and freezer (−18 °C) for further evaluation of their properties. General grade solvents and reagents were purchased from commercial suppliers and used without further purification. The IR spectra were obtained with a Perkin Elmer 400 Fourier Transform Infrared (FTIR) spectrometer. Both of ^{1}H and ^{13}C-NMR spectra were recorded on Jeol Lambda and ECA-DELTA as well as Bruker spectrometers at 400 MHz, while ^{19}F-NMR was recorded using Bruker spectrometers 400 MHz. High-resolution mass spectra were recorded on Agilent Technologies 6530 Accurate Q-TOF LC–MS system, applying DMSO /MeOH eluents for ILs sample compounds while Agilent 5975 system for EI/MS (NUS, Singapore) for the rest compounds. Thin layer chromatography was carried out on pre-coated silica gel plates (0.25 mm, 20 × 20 cm, 60F254, E. Merck).

5.4.2 Procedure for Synthesis of compound 3

This compound was prepared according to modification applied to a procedure described in literature (Ropponen, Nattinen, Lahtinen, & Rissanen, 2004). 1,1,1-Tris (hydroxylmethyl)ethane **1** (10 g, 83.3 mmol) was dissolved and refluxed with minimum amount of chloroacetyl chloride **2** until all HCl gas was liberated (pursue by wet litmus paper). The reaction mixture was evaporated in *vacuo* until the excess of acid chloride was removed. The crude product was purified by co-evaporation with toluene (4–5 times) to produce pale-yellow viscous syrup solidified after few days. Re-crystallization from dry acetonitrile gave compound **3** as colourless crystals.

Tris-((2-chloro-acetayloxy)methyl)ethane (3): Colourless crystals; Yield: 27.94 g (96%); m.p 42-44°C. Molecular Formula: $C_{11}H_{15}Cl_3O_6$; Mol. Wt.: 349.59; FTIR (cm^{-1}): 2960, 2852 (C-H)$_{Aliph}$, 1732 (C=O), 1174, 1150 (O-C), 789 (C-Cl); ^{1}H-NMR (400 MHz, CDCl$_3$) δ ppm: 4.08 (s, 6H, CH$_2$-Cl), 4.04 (s, 6H, CH$_2$-O), 1.02 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm: 167.00 (C=O), 66.98 (CH$_2$-O), 40.73 (CH$_2$-Cl), 38.42 (-C-), 16.92 (CH$_3$); EIMS (m/z): 347.9 (10%)(M), 273.0 (12%), 197.0 (45%), 121.0 (66%), 90.9 (100%).

5.4.3 General Procedure for Synthesis of 6c-g and 7b-g

These compounds were prepared according to modification applied to a procedure described in literature (Starikova *et al.*, 2003). Potassium hydroxide (8.24 g, 147 mmol) was added to a solution of imidazole (5g) or benzimidazole (8.67g), (73.4 mmol) in DMSO (30 mL) and the mixture was stirred for 30 min at room temperature. The corresponding alkyl halide (61.2 mmol) was added portion-wise under vigorous stirring in a water bath and the stirring was continued overnight. The mixture was quenched with water (200 mL) and extracted with diethyl ether (3 × 25 mL). The combined

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extracts were washed with water, dried over anhydrous magnesium sulphate and the solvent was evaporated off under reduced pressure.

1-Hexyl-1H-imidazole (6c): This compound was prepared by using 1-bromohexane (10.10 g, 8.60 mL, 61.2 mmol) to give pale yellow oil in 91% yield (8.48 g). Molecular Formula: $C_9H_{16}N_2$; Mol. Wt.: 152.24; FTIR (cm^{-1}): 3106 (C-H)$_{Ar}$, 2955, 2929, 2858 (C-H)$_{Aliph}$, 1506 (C=N), 1460 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, CDCl$_3$) δ ppm: 7.29 (s, H, C-H$_{Imidazole}$), 6.88 (s, H, C-H$_{Imidazole}$), 6.75 (s, H, C-H$_{Imidazole}$), 3.76 (t, J = 7.02 Hz, 2H, α-CH$_2$), 1.64-1.56 (m, 2H, β-CH$_2$), 1.13 (bs, 6H, bulk-CH$_2$), 0.72 (t, J = 6.71 Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm: 136.95 (CH$_{Imidazole}$), 129.19 (CH$_{Imidazole}$), 118.75 (CH$_{Imidazole}$), 46.91 (α-CH$_2$), 31.17 (ω-2), 30.98 (bulk-CH$_2$), 26.02 (β), 22.35 (ω-1), 13.90 (ω); EIMS (m/z): 152.1 (15%)(M), 137.0 (3%), 125.1 (35%), 109.1 (6%), 96.0 (19%), 84.0 (89%), 69.0 (23%), 49.0 (100%).

1-Octyl-1H-imidazole (6d): This compound was prepared by using 1-bromooctane (11.82 g, 10.65 mL, 61.2 mmol) to give pale yellow oil in 94% yield (10.37 g). Molecular Formula: $C_{11}H_{20}N_2$; Mol. Wt.: 180.29; FTIR (cm^{-1}): 3108 (C-H)$_{Ar}$, 2958, 2925, 2855 (C-H)$_{Aliph}$, 1677 (C=N), 1506, 1461 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, CDCl$_3$) δ ppm: 7.32 (s, H, C-H$_{Imidazole}$), 6.91 (s, H, C-H$_{Imidazole}$), 6.77 (s, H, C-H$_{Imidazole}$), 3.78 (t, J = 7.07 Hz, 2H, α-CH$_2$), 1.66-1.59 (m, 2H, β-CH$_2$), 1.15 (bs, 10H, bulk-CH$_2$), 0.75 (t, J = 7.07 Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm: 137.04 (CH$_{Imidazole}$), 129.28 (CH$_{Imidazole}$), 118.77 (CH$_{Imidazole}$), 47.01 (α-CH$_2$), 31.72 (ω-2), 30.89, 29.09, 29.02 (bulk-CH$_2$), 26.52 (β), 22.60 (ω-1), 14.06 (ω); EIMS (m/z): 180.1 (45%)(M), 165.1 (10%), 151.1 (24%), 137.1 (20%), 109.1 (36%), 96.0 (40%), 82.0 (100%), 69.0 (55%), 55.0 (25%), 43.1 (18%).

1-Decyl-1H-imidazole (6e): This compound was prepared by using 1-bromodecane (13.54 g, 12.65 mL, 61.2 mmol) to give pale yellow oil in 93% yield (11.86g). Molecular Formula: $C_{13}H_{24}N_2$; Mol. Wt.: 208.34; FTIR (cm^{-1}): 3107 (C-H)$_{Ar}$,

2956, 2925, 2855 (C-H)$_{Aliph}$, 1678(C=N), 1506, 1461 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, CDCl$_3$) δ ppm: 7.38 (s, H, C-H$_{Imidazole}$), 6.97 (s, H, C-H$_{Imidazole}$), 6.83 (s, H, C-H$_{Imidazole}$), 3.85 (t, J = 7.07 Hz, 2H, α-CH$_2$), 1.73-1.66 (m, 2H, β-CH$_2$), 1.19 (bs, 14H, bulk-CH$_2$), 0.81 (t, J = 7.07Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm: 137.07 (CH$_{Imidazole}$), 129.33 (CH$_{Imidazole}$), 118.79 (CH$_{Imidazole}$), 47.06 (α-CH$_2$), 31.88 (ω-2), 31.11, 29.50, 29.46, 29.28, 29.10 (bulk -CH$_2$), 26.57 (β), 22.69 (ω-1), 14.13(ω); EIMS (m/z): 207.2 (32%)(M$^+$), 193.1 (9%), 179.1 (18%), 165.1 (14%), 151.1 (18%), 137.1 (23%), 123.1 (35%), 109.1 (28%), 96.0 (48%), 82.0 (100%), 69.0 (48%), 55.0 (45%), 43.1 (29%).

1-Dodecyl-1H-imidazole (6f): This compound was prepared by using 1-bromododecane (15.25 g, 14.7 mL, 61.2 mmol) to give pale yellow oil in 96% yield (13.88 g). Molecular Formula: C$_{15}$H$_{28}$N$_2$; Mol. Wt.: 236.40; FTIR (cm^{-1}): 3010 (C-H)$_{Ar}$, 2955, 2924, 2854 (C-H)$_{Aliph}$, 1672 (C=N), 1505, 1495, 1452 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, CDCl$_3$) δ ppm: 7.29 (s, H, C-H$_{Imidazole}$), 6.88 (s, H, C-H$_{Imidazole}$), 6.74 (s, H, C-H$_{Imidazole}$), 3.76 (t, J = 7.09 Hz, 2H, α-CH$_2$), 1.64-1.57 (m, 2H, β-CH$_2$), 1.11 (bs, 18H, bulk-CH$_2$), 0.74 (t, J = 7.09 Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm: 136.26 (CH$_{Imidazole}$), 128.89 (CH$_{Imidazole}$), 118.34 (CH$_{Imidazole}$), 46.60 (α-CH$_2$), 31.52 (ω-2), 30.70, 29.22 (2), 29.13, 29.04, 28.95, 28.68 (bulk-CH$_2$), 26.15 (β), 22.29 (ω-1), 13.71 (ω); EIMS (m/z): 235.2 (40%)(M$^+$), 221.2 (32%), 207.2 (38%), 193.1 (22%), 179.1 (28%), 165.1 (14%), 151.1 (25%), 137.1 (18%), 123.1 (35%), 109.1 (30%), 96.0 (48%), 82.0 (100%), 69.0 (35%), 55.0 (45%), 43.1 (35%).

1-Benzyl-1H-imidazole (6g): This compound was prepared by using benzyl bromide (10.47 g, 7.28 mL, 61.2 mmol) to give brown viscous syrup crystallized after 5-7 days. Re-crystallization from hexane gave off-white crystals in 86% yield (7.75 g); m.p 70-72°C. Molecular Formula: C$_{10}$H$_{10}$N$_2$; Mol. Wt.: 158.20; FTIR (cm^{-1}): 3113, 3028 (C-H)$_{Ar}$, 2942 (C-H)$_{Aliph}$, 1664, 1603, 1585 (C=N), 1505, 1495, 1449 (C=C)$_{Ar}$; ^{1}H-

NMR (400 MHz, DMSO-d_6) δ ppm: 7.74 (s, H, C-H$_{Imidazole}$), 7.46-7.17 (m, 6H, 5H$_{Ar}$, C-H$_{Imidazole}$), 6.90 (s, H, C-H$_{Imidazole}$), 5.18 (s, 2H, Ar-C$\underline{H}_2$-N); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 137.91 (-$\underline{C}_{Ar}$-CH$_2$-), 137.80 (CH$_{Imidazole}$), 129.22 (2CH$_{Ar}$), 128.89 (CH$_{Imidazole}$), 128.35 (CH$_{Ar}$), 128.05 (2CH$_{Ar}$), 120.19 (CH$_{Imidazole}$), 50.13 (Ar-$\underline{C}$H$_2$-); EIMS (m/z): 158.0 (15%)(M), 131.0 (10%), 118.0 (15%), 104.0 (11%), 91.0 (100%), 77.0 (7.5%), 65.0 (14%).

1-Butyl-1H-benzimidazole (7b): This compound was prepared by using 1-bromobutane (8.38 g, 6.57 mL, 61.2 mmol) to give yellow oil in 83% yield (8.84 g). Molecular Formula: C$_{11}$H$_{14}$N$_2$; Mol. Wt.: 174.24; FTIR (cm^{-1}): 3055 (C-H)$_{Ar}$, 2955, 2930, 2855 (C-H)$_{Aliph}$, 1612 (C=N), 1494, 1450 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.21 (s, H, C-H$_{BImidazole}$), 7.64 (d, J= 8.05 Hz, H, C-H$_{Ar}$), 7.58 (d, J= 8.05 Hz, H, C-H$_{Ar}$), 7.26-7.16 (m, 2H, CH$_{Ar}$), 4.23 (t, J= 7.07 Hz, 2H, α-CH$_2$), 1.72-1.79 (m, 2H, β-CH$_2$), 1.28-1.18 (m, 2H, (ω-1)), 0.87 (t, J =7.23 Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 144.49 (CH$_{BImidazole}$), 144.07 (C$_{Ar}$), 134.35 (C$_{Ar}$), 122.68 (CH$_{Ar}$), 121.85 (CH$_{Ar}$), 119.97 (CH$_{Ar}$), 110.82 (CH$_{Ar}$), 44.30 (α-CH$_2$), 31.98 (ω-2), 19.87 (ω-1), 13.86 (ω); EIMS (m/z): 174.1 (50%)(M), 159.0 (12%), 145.0 (18%), 131.0 (100%), 118.0 (30%), 104.0 (12%), 90.0 (10%) 77.0 (25%).

1-Hexyl-1H-benzimidazole (7c): This compound was prepared by using 1-bromohexane (10.10 g, 8.63 mL, 61.2 mmol) to give yellow oil in 88% yield (10.90 g). Molecular Formula: C$_{13}$H$_{18}$N$_2$; Mol. Wt.: 202.30; FTIR (cm^{-1}): 3058 (C-H)$_{Ar}$, 2954, 2928, 2857 (C-H)$_{Aliph}$, 1615 (C=N), 1494, 1457 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.23 (s, H, C-H$_{BImidazole}$), 7.69 (d, J= 7.56 Hz, H, C-H$_{Ar}$), 7.54 (d, J= 7.56 Hz, H, C-H$_{Ar}$), 7.25-7.17 (m, 2H, CH$_{Ar}$), 4.18 (t, J= 7.07 Hz, 2H, α-CH$_2$), 1.76-1.69 (m, β-CH$_2$), 1.18 (bs, 6H, bulk-CH$_2$), 0.78 (t, J = 6.34 Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 143.86 (CH$_{BImidazole}$), 143.55 (C$_{Ar}$), 133.77 (C$_{Ar}$), 122.05 (CH$_{Ar}$), 121.22 (CH$_{Ar}$), 119.40 (CH$_{Ar}$), 110.17 (CH$_{Ar}$), 44.02 (α-CH$_2$), 30.67 (ω-2), 29.32 (bulk-

CH$_2$), 25.73 (β), 21.93 (ω-1), 13.78 (ω); EIMS (m/z): 202.1 (43%)(M), 187.1 (5%), 173.1 (18%), 159.0 (15%), 145.0 (15%), 131.0 (100%), 118.0 (19%), 104.0 (12%), 90.0 (7%) 77.0 (17%).

1-Octyl-1H-benzimidazole (7d): This compound was prepared by using 1-bromooctane (11.82 g, 10.65 mL, 61.2 mmol) to give yellow oil in 90% yield (12.69 g). Molecular Formula: C$_{15}$H$_{22}$N$_2$; Mol. Wt.: 230.35; FTIR (cm^{-1}): 3058(C-H)$_{Ar}$, 2955, 2925, 2854 (C-H)$_{Aliph}$, 1615 (C=N), 1494, 1458 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.21 (s, H, C-H$_{BImidazole}$), 7.64 (d, J= 7.07 Hz, H, C-H$_{Ar}$), 7.56 (d, J= 7.07 Hz, H, C-H$_{Ar}$), 7.25-7.16 (m, 2H, CH$_{Ar}$), 4.20 (t, J= 7.07 Hz, 2H, α-CH$_2$), 1.79-1.72 (m, β-CH$_2$), 1.17 (bs, 10H, bulk-CH$_2$), 0.80 (t, J = 7.07 Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 144.39 (CH$_{BImidazole}$), 144.06 (C$_{Ar}$), 134.29 (C$_{Ar}$), 122.60 (CH$_{Ar}$), 121.77 (CH$_{Ar}$), 119.94 (CH$_{Ar}$), 110.69 (CH$_{Ar}$), 44.58 (α-CH$_2$), 31.72 (ω-2), 29.92, 29.14, 29.05 (bulk-CH$_2$), 26.66 (β), 22.59 (ω-1), 14.32 (ω); EIMS (m/z): 230.1 (40%)(M), 215.1 (9%), 201.1 (12%), 187.1 (24%), 173.1 (39%), 159.0 (25%), 145.0 (39%), 131.0 (100%), 118.0 (47%), 104.0 (17%), 90.0 (9%), 77.0 (22%).

1-Decyl-1H-benzimidazole (7e): This compound was prepared by using 1-bromodecane (13.53 g, 12.65 mL, 61.2 mmol) to give a yellow semi-solid in 91% yield (14.38 g). Molecular Formula: C$_{17}$H$_{26}$N$_2$; Mol. Wt.: 258.40; FTIR (cm^{-1}): 3057 (C-H)$_{Ar}$, 2954, 2923, 2853 (C-H)$_{Aliph}$, 1615 (C=N), 1494,1458 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.20 (s, H, C-H$_{BImidazole}$), 7.64 (d, J= 7.32 Hz, H, C-H$_{Ar}$), 7.56 (d, J= 7.32 Hz, H, C-H$_{Ar}$), 7.25-7.16 (m, 2H, CH$_{Ar}$), 4.21 (t, J= 7.16 Hz, 2H, α-CH$_2$), 1.79-1.72 (m, 2H, β-CH$_2$), 1.18 (bs, 14H, bulk-CH$_2$), 0.82 (t, J = 7.07 Hz, 3H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 144.34 (CH$_{BImidazole}$), 143.40 (C$_{Ar}$), 134.05 (C$_{Ar}$), 122.93 (CH$_{Ar}$), 122.13 (CH$_{Ar}$), 119.73 (CH$_{Ar}$), 110.82 (CH$_{Ar}$), 44.63 (α-CH$_2$), 31.65 (ω-2), 29.69, 29.56, 29.24, 29.02, 28.88 (bulk-CH$_2$), 26.43 (β), 22.48 (ω-1), 14.30 (ω); EIMS (m/z): 258.2 (60%)(M), 243.2 (16%), 229.1 (32%), 215.1 (27%), 201.1 (30%),

187.1 (36%), 173.1 (53%), 159.1 (39%), 145.0 (50%), 131.0 (100%), 118.0 (70%), 104.0 (21%), 90.0 (10%), 77.0 (25%).

1-Dodecyl-1H-benzimidazole (7f): This compound was prepared by using 1-bromododecane (15.25 g, 14.70 mL, 61.2 mmol) to give yellow semi-solid in 94% yield (16.48 g). Molecular Formula: $C_{19}H_{30}N_2$; Mol. Wt.: 286.45; FTIR (cm^{-1}): 3055 (C-H)$_{Ar}$, 2958, 2924, 2857 (C-H)$_{Aliph}$, 1612 (C=N), 1496, 1458 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, CDCl$_3$) δ ppm: 7.84 (s, H, C-H$_{BImidazole}$), 7.82-7.77 (m, H, C-H$_{Ar}$), 7.37-7.34 (m, H, C-H$_{Ar}$), 7.29-7.23 (m, 2H, CH$_{Ar}$), 4.09 (t, J= 7.09 Hz, 2H, α-CH$_2$), 1.87-1.80 (m, 2H, β-CH$_2$), 1.23 (bs, 18H, (bulk-CH$_2$)), 0.87 (t, J = 7.09 Hz, 3H, ω-CH$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm: 143.75 (C$_{Ar}$), 142.74 (CH$_{BImidazole}$), 133.68 (C$_{Ar}$), 122.57 (CH$_{Ar}$), 121.78 (CH$_{Ar}$), 120.17 (CH$_{Ar}$), 109.49 (CH$_{Ar}$), 44.89 (α-CH$_2$), 31.74 (ω-2), 29.62, 29.42 (2), 29.43, 29.25, 29.16, 28.91 (bulk-CH$_2$), 26.63 (β), 22.51 (ω-1), 13.94 (ω). EIMS (m/z): 286.2 (62%)(M), 271.2 (18%), 257.2 (30%), 243.2 (32%), 229.1 (30%), 215.1 (32%), 201.1 (57%), 187.1 (40%), 173.1 (50%), 159.1 (40%), 145.0 (55%), 131.0 (100%), 118.0 (60%), 104.0 (21%), 90.0 (10%), 77.0 (20%).

1-Benzyl-1H-benzimidazole (7g): This compound was prepared by using benzyl bromide (10.47 g, 7.28 mL, 61.2 mmol) to give a brown solid which re-crystallized from hexane gave off-white crystals in 90% yield (11.47 g); m.p 108-110°C. Molecular Formula: $C_{14}H_{12}N_2$; Mol. Wt.: 208.26; FTIR (cm^{-1}): 3081, 3032 (C-H)$_{Ar}$, 2944 (C-H)$_{Aliph}$, 1666, 1613 (C=N), 1493, 1451, 1442 (C=C)$_{Ar}$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.41 (s, H, C-H$_{BImidazole}$), 7.67-7.64 (m, H, C-H$_{Ar}$), 7.51-7.49 (m, H, C-H$_{Ar}$), 7.34-7.14 (m, 7H, C-H$_{Ar}$), 5.49 (s, 2H, Ar-CH$_2$-N); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 144.21 (CH$_{BImidazole}$), 143.57 (C$_{BImidazole}$), 136.93 (-C$_{Ar}$-CH$_2$-), 133.65 (C$_{BImidazole}$), 128.67 (2CH$_{Ar}$), 127.70 (CH$_{Ar}$), 127.35 (2CH$_{Ar}$), 122.37 (CH$_{BImidazole}$), 121.56 (CH$_{BImidazole}$), 119.48 (CH$_{BImidazole}$), 110.67 (CH$_{BImidazole}$), 47.60 (Ar-CH$_2$-); EIMS (m/z): 208.1 (58%)(M), 103.0 (3%), 91.1 (100%), 77.0 (3%), 65.0 (13%).

5.4.4 Synthesis of Tris-((*N*-methyl-imidazoliumyl-acetayloxy)methyl)ethane chloride (8a)

A solution of 1-methylimidazole (1.34 g, 1.3 mL, 16.3 mmol) in acetonitrile anhydrous (5mL) was added drop-wise to a stirred solution of tris-((2-chloro-acetayloxy)methyl)ethane (compound **3**) (1.9g, 5.43 mmol) in acetonitrile anhydrous (15 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred vigorously for 3 hours and refluxed at 50-55 °C for 3–4 days. The acetonitrile top layer was decanted and the IL washed with diethyl ether (3 × 10 mL), then residual solvent removed *in vacuo*. The product was dried at 40 °C, 0.01 mmHg for 48 h to provide a viscous hygroscopic semi-solid in 97% yield (3.14 g). Molecular Formula: $C_{23}H_{33}Cl_3N_6O_6$; Mol. Wt.: 595.90; FTIR (cm^{-1}): 3072 (C-H)$_{Ar}$, 2970, 2925, 2852 (C-H)$_{Aliph}$, 1744 (C=O), 1631 (C=N), 1565, 1464 (C=C)$_{Ar}$, 1214, 1185 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.13 (bt~s, 3H, C-H$_{Imidazole}$, major), 9.10 (bt~s, 3H, C-H$_{Imidazole}$, minor), 7.72 (t, *J* =1.95 Hz, 3H, C-H$_{Imidazole}$, major), 7.70 (t, *J* =1.95 Hz, 3H, C-H$_{Imidazole}$, minor), 7.67 (t, *J* =1.95 Hz, 3H, C-H$_{Imidazole}$, major), 7.65 (t, *J* =1.95 Hz, 3H, C-H$_{Imidazole}$, minor), 5.33 (s, 6H, O-CH$_2$, major), 5.29 (s, 6H, O-CH$_2$, minor), 4.18 (s, 6H, N-CH$_2$), 3.99 (s, 9H, α-CH$_3$, major), 3.94 (s, 9H, α-CH$_3$, minor), 1.09 (s, 3H, CH$_3$, major), 1.07 (s, 3H, CH$_3$, minor); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.81 (C=O, minor), 167.74 (C=O, major), 139.35 (CH$_{Imidazole}$, major), 137.88 (CH$_{Imidazole}$, minor), 125.14 (CH$_{Imidazole}$, major), 124.72 (CH$_{Imidazole}$, major), 124.45 (CH$_{Imidazole}$, minor), 123.36 (CH$_{Imidazole}$, minor), 68.68 (CH$_2$-O, minor), 67.98 (CH$_2$-O, major), 50.85 (CH$_2$-N), 39.90 (-C-), 36.80 (α-CH$_3$, major), 35.10 (α-CH$_3$, minor), 17.11 (CH$_3$, major), 16.99 (CH$_3$, minor); HRMS: m/z, [M^{+3}–2H]−3Cl$^-$ calcd. for $C_{23}H_{31}N_6O_6{}^{5+}$: 487.2305, found: 487.2330.

5.4.5 Synthesis of Tris-((*N*-butyl-imidazoliumyl-acetayloxy)methyl)ethane chloride (8b)

This compound was prepared analogously to **8a** using tris-((2-chloro-acetayloxy)methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-butylimidazole (2.02 g, 2.14 mL,

16.3 mmol) to provide a viscous hygroscopic syrup in 98% yield (3.85 g). Molecular Formula: $C_{32}H_{51}Cl_3N_6O_6$; Mol. Wt.: 722.14; FTIR (cm^{-1}): 3058 (C-H)$_{Ar}$, 2959, 2933, 2873 (C-H)$_{Aliph}$, 1748 (C=O), 1632 (C=N), 1564, 1464 (C=C)$_{Ar}$, 1199, 1165 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.56 (bt~s, 3H, C-H$_{Imidazole}$, major), 9.51 (bt~s, 3H, C-H$_{Imidazole}$, minor), 9.46 (bt~s, 3H, C-H$_{Imidazole}$, minor), 7.89 (dt, J =6.83, 1.71 Hz, 6H, C-H$_{Imidazole}$, major), 7.85 (dt, J =6.83, 1.71 Hz, 6H, C-H$_{Imidazole}$, minor), 5.45 (s, 6H, O-CH$_2$, major), 5.40 (s, 6H, O-CH$_2$, minor), 4.25 (t, J= 7.07 Hz, 6H, α-CH$_2$, major), 4.04 (s, 6H, N-CH$_2$) 3.95 (t, J= 7.07 Hz, 6H, α-CH$_2$, minor), 1.80-1.73 (m, 6H, β-CH$_2$, major), 1.69-1.62 (m, 6H, β-CH$_2$, minor), 1.28-1.14 (m, 6H, (ω-1)), 0.93 (s, 3H, CH$_3$), 0.88 (t, J =7.32 Hz, 9H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.72 (C=O), 137.44 (CH$_{Imidazole}$, major), 137.06 (CH$_{Imidazole}$, minor), 123.95 (CH$_{Imidazole}$), 122.14 (CH$_{Imidazole}$), 66.54 (CH$_2$-O), 49.60 (CH$_2$-N), 48.78 (α-CH$_2$), 38.16 (-C-), 32.56 ((ω-2), minor), 31.40 ((ω-2), major), 19.14 ((ω-1), minor), 18.79 ((ω-1), major), 16.38 (CH$_3$), 13.42 ((ω), minor), 13.32 ((ω), major); HRMS: m/z, [M^{+3}–2H]−3Cl$^-$ calcd. for $C_{32}H_{49}N_6O_6{}^{5+}$: 613.3714, found: 613.3748.

5.4.6 Synthesis of Tris-((*N*-hexyl-imidazoliumyl-acetayloxy)methyl)ethane chloride (8c)

This compound was prepared analogously to **8a** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-hexylimidazole (**6c**) (2.48 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 98% yield (4.29 g). Molecular Formula: $C_{38}H_{63}Cl_3N_6O_6$; Mol. Wt.: 806.30; FTIR (cm^{-1}): 3058 (C-H)$_{Ar}$, 2955, 2929, 2859 (C-H)$_{Aliph}$, 1749 (C=O), 1641 (C=N), 1564, 1463 (C=C)$_{Ar}$, 1192, 1165 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.66 (bt~s, 3H, C-H$_{Imidazole}$, major), 9.60 (bt~s, 3H, C-H$_{Imidazole}$, minor), 9.53 (bt~s, 3H, C-H$_{Imidazole}$, minor), 7.95 (t, J =1.71 Hz, 3H,C-H$_{Imidazole}$, major), 7.90 (t, J =1.71 Hz, 3H,C-H$_{Imidazole}$, major), 7.84 (t, J =1.71 Hz, 3H, Hz, C-H$_{Imidazole}$, minor), 7.80 (t, J =1.71 Hz, 3H, C-H$_{Imidazole}$, minor), 5.50 (s, 6H, O-CH$_2$, major), 5.43 (s, 6H, O-CH$_2$, minor), 4.25 (t, J= 7.07 Hz, 6H,α-CH$_2$, major), 4.16

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(t, *J*= 7.07 Hz, 6H, α-CH$_2$, minor), 4.06 (bs, 6H, N-CH$_2$), 1.81-1.74 (m, 6H, β-CH$_2$), 1.24 (bs, 18H, bulk-CH$_2$), 0.94 (s, 3H, CH$_3$), 0.84 (t, 9H, *J* =6.83 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 168.12 (C=O), 137.33 (CH$_{Imidazole}$, minor), 137.23 (CH$_{Imidazole}$, major), 123.94 (CH$_{Imidazole}$), 122.12 (CH$_{Imidazole}$, minor), 121.98 (CH$_{Imidazole}$, major), 63.98 (CH$_2$-O), 49.78 (CH$_2$-N, major), 49.68 (CH$_2$-N, minor), 49.00 (α-CH$_2$, minor), 48.94 (α-CH$_2$, major)), 40.68 (-C-), 30.52 (ω-2), 29.34 (bulk-CH$_2$), 25.09 (β), 21.91 (ω-1), 16.62 (CH$_3$, minor), 16.47 (CH$_3$, major), 13.84 (ω); HRMS: m/z, [M^{+3}–2H]$^-$3Cl$^-$ calcd. for C$_{38}$H$_{61}$N$_6$O$_6$$^{5+}$: 697.4653, found: 697.4648.

5.4.7 Synthesis of Tris-((*N*-octyl-imidazoliumyl-acetayloxy)methyl)ethane chloride (8d)

This compound was prepared analogously to **8a** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-octylimidazole (**6d**) (2.94 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 97% yield (4.70 g). Molecular Formula: C$_{44}$H$_{75}$Cl$_3$N$_6$O$_6$; Mol. Wt.: 890.46; FTIR (cm^{-1}): 3058 (C-H)$_{Ar}$, 2955, 2925, 2855 (C-H)$_{Aliph}$, 1749 (C=O), 1668 (C=N), 1564, 1464 (C=C)$_{Ar}$, 1199, 1167 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 9.55 (bt~s, 3H, C-H$_{Imidazole}$, major), 9.48 (bt~s, 3H, C-H$_{Imidazole}$, minor), 9.41 (bt~s, 3H, C-H$_{Imidazole}$, minor), 7.89 (dt, 6H, *J* =8.86, 1.72 Hz, C-H$_{Imidazole}$, major), 7.85 (dt , 6H, *J* =8.86, 1.72 Hz, C-H$_{Imidazole}$, minor), 5.45 (s, 6H, O-CH$_2$, major), 5.39 (s, 6H, O-CH$_2$, minor), 5.37 (s, 6H, O-CH$_2$, minor), 4.24 (t, *J*= 7.15 Hz, 6H, α-CH$_2$), 4.06 (bs, 6H, N-CH$_2$), 1.82-1.74 (m, 6H, β-CH$_2$), 1.24 (bs, 30H, bulk-CH$_2$), 0.95 (s, 3H, CH$_3$), 0.85 (t, *J* =6.98 Hz, 9H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 167.99 (C=O, major), 166.85 (C=O, minor), 137.31 (CH$_{Imidazole}$, minor), 137.21 (CH$_{Imidazole}$, major), 123.87 (CH$_{Imidazole}$), 122.05 (CH$_{Imidazole}$, minor), 121.91 (CH$_{Imidazole}$, major), 63.92 (CH$_2$-O, major), 63.05 (CH$_2$-O, minor), 49.75 (CH$_2$-N, major), 49.63 (CH$_2$-N, minor), 48.94 (α-CH$_2$, minor), 48.87 (α-CH$_2$, major), 40.62 (-C-), 31.10 (ω-2), 29.34, 28.44, 28.26 ((bulk-CH$_2$), 25.39 (β), 22.01 (ω-1), 16.57 (CH$_3$,

major), 16.42 (CH_3, minor), 13.89 (ω); HRMS: m/z, $[M^{+3}-2H]-3Cl^-$ calcd. for $C_{44}H_{73}N_6O_6^{5+}$: 781.5592, found: 781.5608.

5.4.8 Synthesis of Tris-((*N*-decyl-imidazoliumyl-acetayloxy)methyl)ethane chloride (8e)

This compound was prepared analogously to **8a** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-decylimidazole (**6e**) (3.39 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 99% yield (5.24 g).Molecular Formula: $C_{50}H_{87}Cl_3N_6O_6$; Mol. Wt.: 974.62; FTIR (cm^{-1}): 3058 (C-H)$_{Ar}$, 2955, 2929, 2857 (C-H)$_{Aliph}$, 1749 (C=O), 1666 (C=N), 1564, 1462 (C=C)$_{Ar}$, 1199, 1165 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.64 (bt~s, 3H, C-H$_{Imidazole}$, major), 9.57 (bt~s, 3H, C-H$_{Imidazole}$, minor), 9.51 (bt~s, 3H, C-H$_{Imidazole}$, minor), 7.94 (t, J =1.81 Hz, 6H, C-H$_{Imidazole}$, major), 7.89 (t, J =1.81 Hz, 6H, C-H$_{Imidazole}$, major), 7.84 (t, J =1.81 Hz, 6H, C-H$_{Imidazole}$, minor), 7.81 (t, J =1.81 Hz, 6H, C-H$_{Imidazole}$, minor), 5.49 (s, 6H, O-CH$_2$, major), 5.45 (s, 6H, O-CH$_2$, minor), 5.40 (s, 6H, O-CH$_2$, minor), 4.25 (t, J= 7.25 Hz, 6H, α-CH$_2$, major), 4.05 (s, 6H, N-CH$_2$), 4.01 (t, 6H, J= 7.25 Hz, α-CH$_2$, minor), 1.82-1.75 (m, 6H, β-CH$_2$, major), 1.73-1.67 (m, 6H, β-CH$_2$, minor), 1.24 (bs, 42H, bulk-CH$_2$), 0.95 (s, 3H, CH$_3$), 0.84 (t, 9H, J =6.80 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.72 (C=O), 137.41 (CH$_{Imidazole}$, major), 136.42 (CH$_{Imidazole}$, minor), 123.91 (CH$_{Imidazole}$), 122.04(CH$_{Imidazole}$), 66.48 (CH$_2$-O), 49.52 (CH$_2$-N), 48.92 (α-CH$_2$), 38.08 (-C-), 31.15 (ω-2), 30.16 (minor), 29.40 (major), 28.53, 28.49, 28.37, 28.31 (bulk-CH$_2$), 25.76 (β, minor), 25.47 (β, major), 22.05 (ω-1), 16.39 (CH$_3$), 13.93 (ω); HRMS: m/z, $[M^{+3}-2H]-3Cl^-$ calcd. for $C_{50}H_{85}N_6O_6^{5+}$: 865.6531, found: 865.6518.

5.4.9 Synthesis of Tris-((*N*-dodecyl-imidazoliumyl-acetayloxy)methyl)ethane chloride (8f)

This compound was prepared analogously to **8a** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-dodecylimidazole (**6f**) (3.85 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 99% yield (5.24 g). Molecular

Formula: $C_{56}H_{99}Cl_3N_6O_6$; Mol. Wt.: 1058.78; FTIR (cm⁻¹): 3058 (C-H)_Ar, 2955, 2925, 2859 (C-H)_Aliph, 1749 (C=O), 1677 (C=N), 1564, 1466 (C=C)_Ar, 1199, 1164 (C-O); ¹H-NMR (400 MHz, CD₃OD) δ ppm: 9.20 (bt~s, 3H, C-H_Imidazole, major), 9.14 (bt~s, 3H, C-H_Imidazole, minor), 9.08 (bt~s, 3H, C-H_Imidazole, minor), 7.71 (dt, J =8.15, 1.81 Hz, 6H, C-H_Imidazole, major), 7.67 (dt, 6H, J =8.15, 1.81 Hz, C-H_Imidazole, minor), 5.31 (s, 6H, O-CH₂, major), 5.28 (s, 6H, O-CH₂, minor), 5.26 (s, 6H, O-CH₂, minor), 4.27 (t, J= 7.25 Hz, 6H, α-CH₂, major), 4.23 (t, J= 7.25 Hz, 6H, α-CH₂, minor), 4.18 (s, 6H, N-CH₂, major), 4.14 (s, 6H, N-CH₂, minor), 1.93-1.84 (m, 6H, β-CH₂), 1.26 (bs, 54H, bulk-CH₂), 1.07 (s, 3H, CH₃, major), 1.05 (s, 3H, CH₃, minor), 0.87 (t, 9H, J =6.80 Hz, ω-CH₃); ¹³C-NMR (100 MHz, CD₃OD) δ ppm: 167.87 (C=O, major), 167.78 (C=O, minor), 138.82 (CH_Imidazole), 125.38 (CH_Imidazole), 123.56 (CH_Imidazole), 68.18 (CH₂-O, major), 67.87 (CH₂-O, minor), 67.60 (CH₂-O, minor), 51.22 (CH₂-N), 50.98 (α-CH₂, major), 50.69 (α-CH₂, minor), 39.87 (-C-), 33.17 (ω-2), 31.24, 30.85(2), 30.76, 30.66, 30.57, 30.22 (bulk-CH₂), 27.36 (β), 23.83 (ω-1), 17.24 (CH₃, major), 17.18 (CH₃, minor), 14.56 (ω); HRMS: m/z, [M⁺³–2H]−3Cl⁻ calcd. for $C_{56}H_{97}N_6O_6^{5+}$: 949.7470, found: 949.7479.

5.4.10 Synthesis of Tris-((*N*-benzyl-imidazoliumyl-acetayloxy)methyl)ethane chloride (8g)

This compound was prepared analogously to **8a** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-benzylimidazole (**6g**) (2.58 g, 16.3 mmol) to provide a pale yellow hygroscopic semi-solid in 91% yield (4.12 g). Molecular Formula: $C_{41}H_{45}Cl_3N_6O_6$; Mol. Wt.: 824.19; FTIR (cm⁻¹): 3063 (C-H)_Ar, 2977 (C-H)_Aliph, 1747 (C=O), 1661 (C=N), 1563, 1497 (C=C)_Ar, 1197, 1158 (C-O); ¹H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.69 (s, 3H, C-H_Imidazole, major), 9.57 (s, 3H, C-H_Imidazole, minor), 9.44 (s, 3H, C-H_Imidazole, minor), 7.92 (t, J =1.71, 6H, C-H_Imidazole, major), 7.87 (t, J =1.71, 6H, C-H_Imidazole, minor), 7.45-7.20 (m, 15H, C-H_Ar), 5.56 (s, 6H, Ar-CH₂), 5.47 (s, 6H, O-CH₂, major), 5.42 (s, 6H, O-CH₂, minor), 5.36 (s, 6H, O-

CH$_2$, minor), 4.03 (d~t, 6H, N-CH$_2$), 0.89 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.19 (C=O, minor), 166.64 (C=O, major), 137.54 (CH$_{Imidazole}$), 134.85 (-$\underline{C}_{Ar}$-CH$_2$-), 128.98 (2×CH$_A$), 128.77 (CH$_{Ar}$) 128.39 (2×CH$_{Ar}$), 124.22 (CH$_{Imidazole}$), 122.22 (CH$_{Imidazole}$, minor) 122.15 (CH$_{Imidazole}$, major), 66.48 (CH$_2$-O, major), 66.34 (CH$_2$-O, minor) 51.88 (CH$_2$-N), 49.68 (Ar-CH$_2$-), 41.10 (-C-), 16.31 (CH$_3$, major), 16.20 (CH$_3$, minor); HRMS: m/z, [M^{+3}−2H]−3Cl$^-$ calcd. for C$_{41}$H$_{43}$N$_6$O$_6$$^{5+}$: 715.3244, found: 715.3274.

5.4.11 Synthesis of Tris-((*N*-butyl-benzimidazoliumyl-acetayloxy)methyl)ethane chloride (9b)

To a stirred solution of tris-((2-chloro-acetayloxy)methyl)ethane (compound **3**) (1.9g, 5.43 mmol) in acetonitrile anhydrous (15 mL), the solution of 1-butyl-benzimi-dazole (**7b**) (2.84 g, 16.3 mmol) in acetonitrile anhydrous (5 mL) was added drop-wise at room temperature and under nitrogen atmosphere. The reaction mixture was refluxed at 45-50 °C for 2-3 days, then at room temperature for 5 hours. The acetonitrile top layer was decanted and the IL washed with diethyl ether (3 × 10 mL), then residual solvent was evaporated under reduced pressure. The product was dried at 40 °C, 0.01 mmHg for 72 h to provide viscous hygroscopic syrup in 97% yield (4.65 g). Molecular Formula: C$_{44}$H$_{57}$Cl$_3$N$_6$O$_6$; Mol. Wt.: 872.32; FTIR (cm^{-1}): 3025 (C-H)$_{Ar}$, 2950, 2935, 2862 (C-H)$_{Aliph}$, 1748 (C=O), 1616 (C=N), 1559, 1478, 1460 (C=C)$_{Ar}$, 1197, 1160 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.30 (s, 3H, C-H$_{BImidazole}$, major), 10.23 (s, 3H, C-H$_{BImidazole}$, minor), 10.18 (s, 3H, C-H$_{BImidazole}$, minor), 8.14-8.07 (m, 6H, CH$_{Ar}$), 7.71-7.61 (m, 6H, CH$_{Ar}$), 5.81 (s, 6H, O-CH$_2$, major), 5.76 (s, 6H, O-CH$_2$, minor), 4.58 (t, *J*=6.83, 6H, α-CH$_2$, major), 4.50 (t, *J*=6.83, 6H, α-CH$_2$, minor), 4.05 (s, 6H, N-CH$_2$, minor), 4.00 (s, 6H, N-CH$_2$, major), 1.91-1.83 (m, 6H, β-CH$_2$, major), 1.79-1.72 (m, 6H, β-CH$_2$, minor), 1.36- 1.27 (m, 6H, (ω-1)), 0.89 (t, 9H, *J* =7.32 Hz, ω-CH$_3$), 0.81 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.88 (C=O), 143.37 (CH$_{BImidazole}$, major), 142.97 (CH$_{BImidazole}$, minor), 131.43 (C$_{Ar}$), 129.71 (C$_{Ar}$), 124.80 (CH$_{Ar}$), 124.73

(CH$_{Ar}$), 115.03 (CH$_{Ar}$), 113.12 (CH$_{Ar}$), 66.22 (CH$_2$-O), 47.52 (CH$_2$-N), 45.91 (α-CH$_2$, major), 45.09 (α-CH$_2$, minor), 38.12 (-C-), 32.23 ((ω-2), minor), 31.85 ((ω-2), major), 17.98 ((ω-1), minor), 17.32 ((ω-1), major), 16.15 (CH$_3$), 13.80 ((ω), minor), 13.69 ((ω), major); HRMS: m/z, [M^{+3}–2H]−3Cl$^-$ calcd. for C$_{44}$H$_{55}$N$_6$O$_6$$^{5+}$: 763.4183, found: 763.4223.

5.4.12 Synthesis of Tris-((*N*-hexyl-benzimidazoliumyl-acetayloxy)methyl)ethane chloride (9c)

This compound was prepared analogously to **9b** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-hexyl-benzimidazole (**7c**) (3.30 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 99% yield (5.15 g). Molecular Formula: C$_{50}$H$_{69}$Cl$_3$N$_6$O$_6$; Mol. Wt.: 956.48; FTIR (cm^{-1}): 3020 (C-H)$_{Ar}$, 2954, 2929, 2859 (C-H)$_{Aliph}$, 1748 (C=O), 1617(C=N), 1563, 1486, 1464 (C=C)$_{Ar}$, 1196, 1160 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.39 (s, 3H, C-H$_{BImidazole}$, major), 10.32 (s, 3H, C-H$_{BImidazole}$, minor), 10.26 (s, 3H, C-H$_{BImidazole}$, minor), 8.15-8.09 (m, 6H, CH$_{Ar}$), 7.70-7.61 (m, 6H, CH$_{Ar}$, major), 7.31-7.24 (m, 6H, CH$_{Ar}$, minor), 5.85 (s, 6H, O-CH$_2$, major), 5.80 (s, 6H, O-CH$_2$, minor), 4.57 (t, *J*=7.07, 6H, α-CH$_2$, major), 4.29 (t, *J*=7.07, 6H, α-CH$_2$, minor), 4.03 (s, 6H, N-CH$_2$, minor), 3.99 (s, 6H, N-CH$_2$, major), 1.92-1.84 (m, 6H, β-CH$_2$), 1.26 (bs, 18H, bulk-CH$_2$), 0.86 (s, 3H, CH$_3$), 0.82 (t, 9H, overlap, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.13 (C=O, minor), 166.41 (C=O, major), 143.37 (CH$_{BImidazole}$), 131.50 (C$_{Ar}$), 130.61 (C$_{Ar}$), 126.74 (CH$_{Ar}$), 126.66 (CH$_{Ar}$), 114.10 (CH$_{Ar}$), 113.75 (CH$_{Ar}$), 66.29 (CH$_2$-O), 47.55 (CH$_2$-N), 46.80 (α-CH$_2$), 38.13 (-C-), 30.56 (ω-2), 28.49 (bulk-CH$_2$), 25.64 (β, minor), 25.32 (β, major), 21.87 (ω-1), 16.16 (CH$_3$, major), 16.09 (CH$_3$, minor), 13.79 (ω); HRMS: m/z, [M^{+3}–2H]−3Cl$^-$ calcd. for C$_{50}$H$_{67}$N$_6$O$_6$$^{5+}$: 847.5122, found: 847.5162.

5.4.13 Synthesis of Tris-((*N*-octyl-benzimidazoliumyl-acetayloxy)methyl)ethane chloride (9d)

This compound was prepared analogously to **9b** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-octyl-benzimidazole (**7d**) (3.75 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 98% yield (5.54g). Molecular Formula: $C_{56}H_{81}Cl_3N_6O_6$; Mol. Wt.: 1040.64; FTIR (cm^{-1}): 3134 (C-H)$_{Ar}$, 2955, 2925, 2855 (C-H)$_{Aliph}$, 1749 (C=O), 1618 (C=N), 1562, 1486 1462 (C=C)$_{Ar}$, 1199 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.39 (s, 3H, C-H$_{BImidazole}$, major), 10.32 (s, 3H, C-H$_{BImidazole}$, minor), 10.26 (s, 3H, C-H$_{BImidazole}$, minor), 8.16-8.10 (m, 6H, CH$_{Ar}$), 7.70-7.61 (m, 6H, CH$_{Ar}$, major), 7.29-7.19 (m, 6H, CH$_{Ar}$, minor), 5.85 (s, 6H, O-CH$_2$, major), 5.80 (s, 6H, O-CH$_2$, minor), 4.57 (t, J=7.07, 6H, α-CH$_2$, major), 4.25 (t, J=7.07, 6H, α-CH$_2$, minor), 4.04 (s, 6H, N-CH$_2$, minor), 3.99 (s, 6H, N-CH$_2$, major), 1.92- 1.85 (m, 6H, β-CH$_2$), 1.20 (bs, 30H, bulk-CH$_2$), 0.86 (s, 3H, CH$_3$), 0.82 (t, 9H, J=6.80, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.83 (C=O, major), 166.51 (C=O, minor), 143.22 (CH$_{BImidazole}$), 131.56 (C$_{Ar}$), 130.62 (C$_{Ar}$), 126.79 (CH$_{Ar}$), 126.57 (CH$_{Ar}$), 113.86 (CH$_{Ar}$), 113.71 (CH$_{Ar}$), 64.02 (CH$_2$-O, major), 63.13 (CH$_2$-O, minor), 47.54 (CH$_2$-N), 46.77 (α-CH$_2$), 40.58 (-C-), 31.08 (ω-2), 28.42 (2), 28.31 (bulk-CH$_2$), 25.61 (β), 21.98 (ω-1), 16.55 (CH$_3$, major), 16.32 (CH$_3$, minor), 13.88 (ω); HRMS: m/z, [M^{+3}–2H]−3Cl$^-$ calcd. for $C_{56}H_{79}N_6O_6^{5+}$: 931.6061, found: 931.6144.

5.4.14 Synthesis of Tris-((*N*-decyl-benzimidazoliumyl-acetayloxy)methyl)ethane chloride (9e)

This compound was prepared analogously to **9b** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1- decyl-benzimidazole (**7e**) (4.21 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 99% yield (6.00g). Molecular Formula: $C_{62}H_{93}Cl_3N_6O_6$; Mol. Wt.: 1124.80; FTIR (cm^{-1}): 3134 (C-H)$_{Ar}$, 2958, 2923, 2854 (C-H)$_{Aliph}$, 1749 (C=O), 1619 (C=N), 1562 1485, 1463 (C=C)$_{Ar}$, 1199 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.36 (s, 3H, C-H$_{BImidazole}$, major), 10.22 (s, 3H, C-H$_{BImidazole}$, minor), 10.12 (s, 3H, C-H$_{BImidazole}$, minor), 8.14-8.09 (m, 6H, CH$_{Ar}$), 7.71-

7.61 (m, 6H, CH$_{Ar}$, major), 7.30-7.20 (m, 6H, CH$_{Ar}$, minor), 5.84 (s, 6H, O-CH$_2$, major), 5.78 (s, 6H, O-CH$_2$, minor), 5.73 (s, 6H, O-CH$_2$, minor), 4.56 (t, J=7.25, 6H, α-CH$_2$, major), 4.51 (t, J=7.25, 6H, α-CH$_2$, minor), 4.04 (s, 6H, N-CH$_2$, minor), 3.99 (s, 6H, N-CH$_2$, major), 3.97 (s, 6H, N-CH$_2$, minor), 1.92- 1.85 (m, 6H, β-CH$_2$), 1.20 (bs, 42H, bulk-CH$_2$), 0.86 (s, 3H, CH$_3$), 0.82 (t, 9H, J=6.80, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.17 (C=O, minor), 166.44 (C=O, major), 143.37 (CH$_{BImidazole}$, major), 142.28 (CH$_{BImidazole}$, minor), 131.51 (C$_{Ar}$), 130.63 (C$_{Ar}$), 126.77 (CH$_{Ar}$), 126.69 (CH$_{Ar}$), 114.09 (CH$_{Ar}$, major), 113.99 (CH$_{Ar}$, minor), 113.77 (CH$_{Ar}$), 66.30 (CH$_2$-O, major), 66.17 (CH$_2$-O, minor), 47.53 (CH$_2$-N), 46.82 (α-CH$_2$, major), 46.66 (α-CH$_2$, minor), 38.17 (-C-), 31.29 ((ω-2), major), 30.71 ((ω-2), minor), 28.91, 28.87, 28.68, 28.57, 28.64 (bulk-CH$_2$), 25.71 (β), 22.10 (ω-1), 16.18 (CH$_3$, major), 16.11 (CH$_3$, minor), 13.95 (ω); HRMS: m/z, [M^{+3}–2H]$^-$3Cl$^-$ calcd. for C$_{62}$H$_{91}$N$_6$O$_6$$^{5+}$: 1015.7000, found: 1015.7055.

5.4.15 Synthesis of Tris-((*N*-dodecyl-benzimidazoliumyl-acetayloxy)methyl)ethane chloride (9f)

This compound was prepared analogously to **9b** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-dodecyl-benzimidazole (**7f**) (4.67 g, 16.3 mmol) to provide a viscous hygroscopic syrup in 99% yield (6.50g). Molecular Formula: C$_{68}$H$_{105}$Cl$_3$N$_6$O$_6$; Mol. Wt.: 1208.96; FTIR (cm^{-1}): 3132 (C-H)$_{Ar}$, 2955, 2925, 2855 (C-H)$_{Aliph}$, 1749 (C=O), 1619 (C=N), 1562, 1486, 1455 (C=C)$_{Ar}$, 1198 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.77 (s, 3H, C-H$_{BImidazole}$, major), 9.73 (s, 3H, C-H$_{BImidazole}$, minor), 9.67 (s, 3H, C-H$_{BImidazole}$, minor), 8.02-7.89 (m, 6H, CH$_{Ar}$), 7.73-7.57 (m, 6H, CH$_{Ar}$, major), 7.42-7.33 (m, 6H, CH$_{Ar}$, minor), 5.63 (s, 6H, O-CH$_2$, major), 5.60 (s, 6H, O-CH$_2$, minor), 5.58 (s, 6H, O-CH$_2$, minor), 4.54 (t, J=7.25, 6H, α-CH$_2$, major), 4.34 (t, J=7.25, 6H, α-CH$_2$, minor), 4.20 (s, 6H, N-CH$_2$, minor), 4.17 (s, 6H, N-CH$_2$, major), 4.05 (s, 6H, N-CH$_2$), 2.04- 1.96 (m, 6H, β-CH$_2$), 1.25 (bs, 54H, bulk-CH$_2$), 1.00 (s, 3H, CH$_3$), 0.86 (t, J=7.25, 9H, ω-CH$_3$); ^{13}C-NMR (100 MHz,

CD$_3$OD) δ ppm: 167.54 (C=O, minor), 166.26 (C=O, major), 142.72 (CH$_{BImidazole}$, major), 142.46 (CH$_{BImidazole}$, minor), 131.90 (C$_{Ar}$), 131.09 (C$_{Ar}$), 127.19 (CH$_{Ar}$), 127.09 (CH$_{Ar}$), 113.47 (CH$_{Ar}$), 113.35 (CH$_{Ar}$), 66.59 (CH$_2$-O, minor), 66.48 (CH$_2$-O, major), 66.07 (CH$_2$-O, minor), 45.41 (CH$_2$-N), 40.33 (α-CH$_2$), 38.75 (-C-), 31.75 (ω-2), 29.44 (2), 29.35, 29.25, 29.15, 28.90, 28.87 (bulk-CH$_2$), 26.34 ((β), minor), 26.18 ((β), major), 22.42 (ω-1), 15.72 (CH$_3$), 13.17 (ω); HRMS: m/z, [M^{+3}–2H]−3Cl$^-$ calcd. for C$_{68}$H$_{103}$N$_6$O$_6^{5+}$: 1099.7939, found: 1099.7964.

5.4.16 Synthesis of Tris-((*N*-benzyl-benzimidazoliumyl-acetayloxy)methyl)ethane chloride (9g)

This compound was prepared analogously to **9b** using tris-((2-chloro-acetayloxy)-methyl)ethane (compound **3**) (1.9 g, 5.43 mmol) and 1-benzyl-benzimidazole (**7g**) (3.39 g, 16.3 mmol) to provide a pale yellow hygroscopic semi-solid in 96% yield (5.08g). Molecular Formula: C$_{53}$H$_{51}$Cl$_3$N$_6$O$_6$; Mol. Wt.: 974.37 ; FTIR (cm^{-1}): 3120 (C-H)$_{Ar}$, 2974 (C-H)$_{Aliph}$, 1750 (C=O), 1615 (C=N), 1562, 1486, 1455 (C=C)$_{Ar}$, 1190, 1165 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 10.30 (s, 3H, C-H$_{BImidazole}$, major), 10.23 (s, 3H, C-H$_{BImidazole}$, minor), 10.17 (s, 3H, C-H$_{BImidazole}$, minor), 8.05 (d, *J* =8.31 Hz, 3H, C-H$_{Ar}$), 7.99 (d, *J* =8.31 Hz, 3H, C-H$_{Ar}$), 7.63-7.51 (m, 12H, C-H$_{Ar}$), 7.41-7.31 (m, 9H, C-H$_{Ar}$), 5.89 (s, 6H, CH$_2$-Ar), 5.78 (s, 6H, O-CH$_2$, major), 5.74 (s, 6H, O-CH$_2$, minor), 5.67 (s, 6H, O-CH$_2$, minor), 4.03 (s, 6H, N-CH$_2$, major), 3.97 (s, 6H, N-CH$_2$, minor), 0.88 (s, 3H, CH$_3$, minor), 0.85 (s, 3H, minor), 0.81 (s, 3H, CH$_3$, major); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 167.19 (C=O, minor), 166.45 (C=O, major), 143.97 (CH$_{BImidazole}$, minor), 143.66 (CH$_{BImidazole}$, major), 133.93 (-$\underline{C}_{Ar}$-CH$_2$-), 131.65 (C$_{BImidazole}$), 130.34 (C$_{BImidazole}$), 129.00 (2×CH$_{Ar}$), 128.77 (CH$_{Ar}$, major), 128.70 (CH$_{Ar}$, minor), 128.35 (2×CH$_{Ar}$), 126.90 (CH$_{BImidazole}$), 126.84 (CH$_{BImidazole}$), 114.20 (CH$_{BImidazole}$), 113.96 (CH$_{BImidazole}$), 66.36 (CH$_2$-O, major), 66.19 (CH$_2$-O, minor), 49.93 (CH$_2$-N), 47.84 (Ar-CH$_2$-, minor), 47.20 (Ar-CH$_2$-, major), 38.30 (-C-), 16.21 (CH$_3$,

minor), 16.13 (CH$_3$, major); HRMS: m/z, [M^{+3}–2H]−3Cl$^-$ calcd. for C$_{53}$H$_{49}$N$_6$O$_6$$^{5+}$:865.3714, found: 865.3746.

5.4.17 Synthesis of Tris-((*N*-methyl-imidazoliumyl-acetayloxy)methyl)ethane bis-(trifluoromethylsulphonyl)amide (10a)

A flask was charged with tris-((*N*-methyl-imidazoliumyl-acetayloxy)methyl)ethane chloride **8a** (0.6 g, 1.0 mmol) and deionized water (10 mL). Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) in deionized water (3 mL) was added in one portion and the suspension was stirred vigorously for 7 h at room temperature. The mixture was extracted with Ethyl acetate (3×5mL) after stirring for 1h each time. The combined organic layers were evaporated on the rotary evaporator and under high vacuum for 8 h to remove the solvent and produce a clear viscous hygroscopic liquid at room temperature in 81% yield (1.08 g). Molecular Formula: C$_{29}$H$_{33}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1329.98; FTIR (cm^{-1}): 3070 (C-H)$_{Ar}$, 2970, 2932, 2857 (C-H)$_{Aliph}$, 1750 (C=O), 1642 (C=N), 1555, 1468 (C=C)$_{Ar}$, 1359, 1220 (C-F), 1362, 1150 (O=S=O), 1220, 1184(C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 8.70 (s, 3H, C-H$_{Imidazole}$, minor), 8.68 (s, 3H, C-H$_{Imidazole}$, minor), 8.66 (s, 3H, C-H$_{Imidazole}$, major), 7.39 (dt, 6H, *J* =10.79, 1.76, Hz, C-H$_{Imidazole}$), 4.98 (s, 6H, O-CH$_2$, major), 4.97 (s, 6H, O-CH$_2$, minor), 4.94 (s, 6H, O-CH$_2$, minor), 3.98 (s, 6H, N-CH$_2$, major), 3.95 (s, 6H, N-CH$_2$, minor), 3.93 (s, 6H, N-CH$_2$, minor), 3.75 (s, 9H, α-CH$_3$), 0.87 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.90 (C=O, minor), 167.75 (C=O, major), 139.32 (CH$_{Imidazole}$), 126.07, 122.89, 119.71, 116.52 (q, *J*=320, CF$_3$), 125.22 (CH$_{Imidazole}$), 124.91 (CH$_{Imidazole}$), 68.76 (CH$_2$-O, minor), 68.00 (CH$_2$-O, major), 50.82 (CH$_2$-N), 40.19 (-C-), 36.85 (α-CH$_3$), 17.03 (CH$_3$); ^{19}F (336, MHz) δ ppm: –80.12; HRMS: m/z, [M^{+3}–2H]−3NTF$_2$$^-$ calcd. for C$_{23}$H$_{31}$N$_6$O$_6$$^{5+}$: 487.2305, found: 487.2285; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9169.

5.4.18 Synthesis of Tris-((*N*-butyl-imidazoliumyl-acetayloxy)methyl)ethane bis(tri-fluoromethylsulphonyl)amide (10b)

This compound was prepared analogously to **10a** using tris-((*N*-butyl-imidazoliumyl-acetayloxy)methyl)ethane chloride **8b** (0.72 g, 1.0 mmole) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 84% yield (1.22 g). Molecular Formula: C$_{38}$H$_{51}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1456.22; FTIR (cm^{-1}): 3055 (C-H)$_{Ar}$, 2960, 2935, 2872 (C-H)$_{Aliph}$, 1743 (C=O), 1642 (C=N), 1560, 1466 (C=C)$_{Ar}$, 1351, 1223 (C-F), 1360, 1152 (O=S=O), 1195, 1163 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 8.97 (s, 3H, C-H$_{Imidazole}$, minor), 8.94 (s, 3H, C-H$_{Imidazole}$, major), 8.80 (s, 3H, C-H$_{Imidazole}$, minor), 7.70 (s, 3H, C-H$_{Imidazole}$), 7.60 (s, 3H, C-H$_{Imidazole}$, major), 7.50 (s, 3H, C-H$_{Imidazole}$, minor), 5.20 (s, 6H, O-CH$_2$, major), 5.19 (s, 6H, O-CH$_2$, minor), 4.26 (t, *J*= 7.28 Hz, 6H, α-CH$_2$), 4.19 (s, 6H, N-CH$_2$, major), 4.16 (s, 6H, N-CH$_2$, minor), 4.15 (s, 6H, N-CH$_2$, minor), 1.80-1.73 (m, 6H, β-CH$_2$, major), 1.92-1.83 (m, 6H, β-CH$_2$), 1.42-1.33 (m, 6H, (ω-1), 1.08 (s, 3H, CH$_3$), 0.98 (t, *J* =7.28 Hz, 9H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.90 (C=O, minor), 167.77 (C=O, major), 138.67 (CH$_{Imidazole}$), 126.10, 122.91, 119.72, 116.54 (q, *J*=320, CF$_3$), 125.37 (CH$_{Imidazole}$), 123.69 (CH$_{Imidazole}$), 68.83 (CH$_2$-O, minor), 68.30 (CH$_2$-O, minor), 68.10 (CH$_2$-O, major), 51.03 (CH$_2$-N), 50.87 (α-CH$_2$), 40.10 (-C-), 33.39 ((ω-2), minor), 33.15 ((ω-2), major), 20.61 ((ω-1), minor), 20.52 ((ω-1), major), 17.04 (CH$_3$, major), 17.00 (CH$_3$, minor),13.83 (ω); ^{19}F (336, MHz) δ ppm: −80.02; HRMS: m/z, [M^{+3}−2H]−3NTF$_2^-$ calcd. for C$_{32}$H$_{49}$N$_6$O$_6^{5+}$: 613.3714, found: 613.3692; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2^-$: 279.9173, found: 279.9175.

5.4.19 Synthesis of Tris-((*N*-hexyl-imidazoliumyl-acetayloxy)methyl)ethane bis(tri-fluoromethylsulphonyl)amide (10c)

This compound was prepared analogously to **10a** using tris-((*N*-hexyl-imidazoliumyl-acetayloxy)methyl)ethane chloride **8c** (0.81 g, 1.0 mmol) and Lithium bis-(trifluoro-

methanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 85% yield (1.32 g). Molecular Formula: C$_{44}$H$_{63}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1540.38; FTIR (cm^{-1}): 3062 (C-H)$_{Ar}$, 2950, 2931, 2845 (C-H)$_{Aliph}$, 1749 (C=O), 1644 (C=N), 1564, 1460(C=C)$_{Ar}$, 1347, 1220 (C-F), 1366, 1153 (O=S=O), 1185, 1185 (C-O);^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 8.98 (bt~s, 3H, C-H$_{Imidazole}$, minor), 8.96 (bt~s, 3H, C-H$_{Imidazole}$, minor), 8.93 (bt~s, 3H, C-H$_{Imidazole}$, major), 7.69 (t, J =1.81 Hz, 3H, C-H$_{Imidazole}$, major), 7.63 (t, J =1.81 Hz, 3H, C-H$_{Imidazole}$, minor), 7.61 (t, 3H, J =1.81 Hz, C-H$_{Imidazole}$, minor), 7.59 (t, J =1.81 Hz, 3H,C-H$_{Imidazole}$, major), 5.19 (s, 6H, O-CH$_2$), 4.24 (t, J= 7.25 Hz, 6H, α-CH$_2$), 4.19 (s, 6H, N-CH$_2$, major), 4.14 (s, 6H, N-CH$_2$, minor), 1.93-1.86 (m, 6H, β-CH$_2$), 1.34 (bs, 18H, bulk-CH$_2$), 1.08 (s, 3H, CH$_3$), 0.90 (t, J =6.34 Hz, 9H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.77 (C=O), 138.65 (CH$_{Imidazole}$), 126.15, 122.93, 119,71, 116.49 (q, J=320, CF$_3$), 125.37 (CH$_{Imidazole}$), 123.69 (CH$_{Imidazole}$), 68.23 (CH$_2$-O, minor), 68.15 (CH$_2$-O, major), 51.31 (CH$_2$-N), 50.89 (α-CH$_2$), 40.11(-C-), 32.35 (ω-2), 31.14 (bulk-CH$_2$), 26.99 (β-CH$_2$), 23.58 (ω-1), 17.11 (CH$_3$, minor), 17.07 (CH$_3$, major), 14.38 (ω); ^{19}F (336, MHz) δ ppm: −80.22; HRMS: m/z, [M^{+3}–2H]−3NTF$_2^-$ calcd. for C$_{38}$H$_{61}$N$_6$O$_6^{5+}$: 697.4653, found: 697.4623; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2^-$: 279.9173, found: 279.9177.

5.4.20 Synthesis of Tris-((*N*-decyl-imidazoliumyl-acetayloxy)methyl)ethane bis(tri-fluoromethylsulphonyl)amide (10e)

This compound was prepared analogously to **10a** using tris-((*N*-decyl-imidazoliumyl -acetayloxy)methyl)ethane chloride **8e** (0.97 g, 1.0 mmol) and Lithium bis-(trifluoro-methanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 94% yield (1.6 g). Molecular Formula: C$_{56}$H$_{87}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1708.70; FTIR (cm^{-1}): 3058 (C-H)$_{Ar}$, 2955, 2929, 2857 (C-H)$_{Aliph}$, 1749 (C=O), 1666 (C=N), 1564, 1462 (C=C)$_{Ar}$, 1340, 1210 (C-F), 1360, 1123 (O=S=O), 1199, 1165 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.00 (bt~s,

3H, C-H$_{Imidazole}$, minor), 8.98 (bt~s, 3H, C-H$_{Imidazole}$, minor), 8.95 (bt~s, 3H, C-H$_{Imidazole}$, major), 7.70 (t, J=1.81, 3H, C-H$_{Imidazole}$, major), 7.65 (t, 3H, C-H$_{Imidazole}$, minor), 7.61 (t, J=1.81, 3H, C-H$_{Imidazole}$, major), 7.56 (t, 3H, J=1.81, C-H$_{Imidazole}$, minor), 5.31 (s, 6H, O-CH$_2$, minor), 5.21 (s, 6H, O-CH$_2$, major), 4.25 (t, J= 7.25 Hz, 6H, α-CH$_2$), 4.21 (s, 6H, N-CH$_2$), 4.19 (s, 6H, N-CH$_2$), 1.94-1.87 (m, 6H, β-CH$_2$), 1.33 (bs, 42H, bulk-CH$_2$), 1.09 (s, 3H, CH$_3$, major), 1.07 (s, 3H, CH$_3$, minor), 0.90 (t, 9H, J =6.80 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.80 (C=O), 138.67 (CH$_{Imidazole}$), 126.17, 122.94, 119.71, 116.49 (q, J=321, CF$_3$), 125.38 (CH$_{Imidazole}$), 123.70 (CH$_{Imidazole}$), 68.17 (CH$_2$-O), 51.32 (CH$_2$-N), 50.88 (α-CH$_2$), 40.12 (-C-), 33.00 (ω-2), 31.20, 30.30 (2), 30.15 (2) (bulk-CH$_2$), 27.33 (β), 23.80 (ω-1), 17.07 (CH$_3$), 14.53 (ω); ^{19}F (336, MHz) δ ppm: −80.52; HRMS: m/z, [M^{+3}−2H]−3NTF$_2^-$ calcd. for C$_{50}$H$_{85}$N$_6$O$_6^{5+}$ 865.6531 found: 865.6512; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2^-$: 279.9173, found: 279.9148.

5.4.21 Synthesis of Tris-((*N*-benzyl-imidazoliumyl-acetayloxy)methyl)ethane bis-(trifluoromethylsulphonyl)amide (10g)

This compound was prepared analogously to **10a** using tris-((*N*-benzyl-imidazol-iumyl-acetayloxy)methyl)ethane chloride **8g** (0.82 g, 1.0 mmol) and Lithium bis-(trifl-uoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 91% yield (1.41 g). Molecular Formula: C$_{47}$H$_{45}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1558.27; FTIR (cm^{-1}): 3070 (C-H)$_{Ar}$, 2990 (C-H)$_{Aliph}$, 1750 (C=O), 1661 (C=N), 1555, 1487 (C=C)$_{Ar}$, 1340, 1210 (C-F), 1372, 1154 (O=S=O), 1207, 1169 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.05 (s, 3H, C-H$_{Imidazole}$, minor), 9.03 (s, 3H, C-H$_{Imidazole}$, minor), 9.01 (s, 3H, C-H$_{Imidazole}$, major), 7.67 (bt~s, 6H, C-H$_{Imidazole}$, minor), 7.63 (bt~s, 6H, C-H$_{Imi}$, major), 7.59 (bt~s, 6H, C-H$_{Imidazole}$, minor), 7.43-7.21 (m, 15H, C-H$_{Ar}$), 5.45 (s, 6H, Ar-CH$_2$, minor), 5.43 (s, 6H, Ar-CH$_2$, major), 5.19 (s, 6H, O-CH$_2$), 4.18 (s, 6H, N-CH$_2$, minor), 4.15 (s, 6H, N-CH$_2$, major), 4.13 (s, 6H, N-CH$_2$, minor), 1.05 (s, 3H, CH$_3$, minor), 1.03 (s, 3H, CH$_3$, minor), 1.01 (s, 3H, CH$_3$, major); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.74 (C=O, major),

167.69 (C=O, minor), 138.88 (CH$_{Imidazole}$, minor), 138.79 (CH$_{Imidazole}$, major), 135.05 (-$\underline{C}_{Ar}$-CH$_2$-), 130.66 (2×CH$_A$), 129.88 (2×CH$_A$), 126.09, 122.91, 119.73, 116.55 (q, J=319, CF$_3$), 125.65 (CH$_{Imidazole}$), 123.71 (CH$_{Imidazole}$), 68.15 (CH$_2$-O, minor), 68.01 (CH$_2$-O, major), 67.43 (CH$_2$-O, minor), 54.49 (CH$_2$-N), 50.97 (Ar-CH$_2$-), 40.14 (-C-), 17.07 (CH$_3$, minor), 17.00 (CH$_3$, major); ^{19}F (336, MHz) δ ppm: −79.97; HRMS: m/z, [M^{+3}−2H]−3NTF$_2^{-}$ calcd. for C$_{41}$H$_{43}$N$_6$O$_6^{5+}$: 715.3244, found: 715.3281; m/z, [NTF$_2$]$^{-}$ calcd. for C$_2$F$_6$NO$_4$S$_2^{-}$: 279.9173, found: 279.9164.

5.4.22 Synthesis of Tris-((*N*-butyl-benzimidazoliumyl-acetayloxy)methyl)ethane bis(trifluoromethylsulphonyl)amide (11b)

This compound was prepared analogously to **10a** using tris-((*N*-butyl-benzimidazol-iumyl-acetayloxy)methyl)ethane chloride **9b** (0.87 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 84% yield (1.35 g). Molecular Formula: C$_{50}$H$_{57}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1606.39; FTIR (cm^{-1}): 3022 (C-H)$_{Ar}$, 2950, 2942, 2863 (C-H)$_{Aliph}$, 1755(C=O), 1618(C=N), 1564, 1485, 1469 (C=C)$_{Ar}$, 1374, 1233 (C-F), 1354, 1169 (O=S=O), 1187, 1160 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.94 (s, 3H, C-H$_{BImidazole}$, minor), 9.89 (s, 3H, C-H$_{BImidazole}$, minor), 9.82 (s, 3H, C-H$_{BImidazole}$), 8.10-8.04 (m, 6H, CH$_{Ar}$), 7.68-7.59 (m, 6H, CH$_{Ar}$, major), 7.27-7.22 (m, 6H, CH$_{Ar}$, minor), 5.65 (s, 6H, O-CH$_2$, minor), 5.60 (s, 6H, O-CH$_2$, major), 4.47 (t, J=7.07, 6H, α-CH$_2$, major), 4.27 (t, J=7.07, 6H, α-CH$_2$, minor), 4.01 (s, 6H, N-CH$_2$, major), 3.98 (s, 6H, N-CH$_2$, minor), 1.87-1.79 (m, 6H, β-CH$_2$, major), 1.66-1.59 (m, 6H, β-CH$_2$, minor), 1.28-1.18 (m, 6H, (ω-1)), 0.93 (s, 3H, CH$_3$), 0.87 (t, 9H, J =7.21 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.76 (C=O), 144.03 (CH$_{BImidazole}$, major), 143.867 (CH$_{BImidazole}$, minor), 132.45 (C$_{Ar}$), 128.90 (C$_{Ar}$), 125.30, 122.09, 118.88, 115.67 (q, J=321, CF$_3$), 125.02 (CH$_{Ar}$), 124.14 (CH$_{Ar}$), 112.85 (CH$_{Ar}$), 110.17 (CH$_{Ar}$), 68.03 (CH$_2$-O), 46.55 (CH$_2$-N), 44.03 (α-CH$_2$, minor), 43.78 (α-CH$_2$, major), 38.31 (-C-), 32.17 ((ω-2), minor), 31.90 ((ω-2), major), 18.55 ((ω-1), major), 17.95 ((ω-1), minor), 15.74

(CH$_3$), 13.23 ((ω), minor), 13.12 ((ω), major); ^{19}F (336, MHz) δ ppm: −80.12; HRMS: m/z, [M^{+3}–2H]−3NTF$_2$$^-$ calcd. for C$_{44}$H$_{55}$N$_6$O$_6$$^{5+}$: 763.4183, found: 763.4202; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9209.

5.4.23 Synthesis of Tris-((*N*-octyl-benzimidazoliumyl-acetayloxy)methyl)ethane bis(trifluoromethylsulphonyl)amide (11d)

This compound was prepared analogously to **10a** using tris-((*N*-octyl-benzimidazol-iumyl-acetayloxy)methyl)ethane chloride **9d** (1.04 g, 1.0 mmol) and Lithium bis-(trifl-uoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 90% yield (1.60 g). Molecular Formula: C$_{62}$H$_{81}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1774.71; FTIR (cm^{-1}): 3120 (C-H)$_{Ar}$, 2945, 2920, 2850 (C-H)$_{Aliph}$, 1742 (C=O), 1618 (C=N), 1566, 1483 1460 (C=C)$_{Ar}$, 1360, 1220 (C-F), 1350, 1172 (O=S=O), 1192(C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (s, 3H, C-H$_{BImidazole}$, major), 9.97 (s, 3H, C-H$_{BImidazole}$, minor), 9.91 (s, 3H, C-H$_{BImidazole}$, minor), 8.13-8.05 (m, 6H, CH$_{Ar}$), 7.54-7.45 (m, 6H, CH$_{Ar}$, minor), 7.12-7.03 (m, 6H, CH$_{Ar}$, major), 5.83 (s, 6H, O-CH$_2$, major), 5.79 (s, 6H, O-CH$_2$, minor), 4.37 (t, J=7.07, 6H, α-CH$_2$, major), 4.29 (t, J=7.07, 6H, α-CH$_2$, minor), 4.02 (s, 6H, N-CH$_2$, minor), 3.97 (s, 6H, N-CH$_2$, major), 1.92-1.86 (m, 6H, β-CH$_2$), 1.22 (bs, 30H, bulk-CH$_2$), 0.85 (s, 3H, CH$_3$), 0.80 (t, 9H, J=6.80, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 168.10 (C=O, major), 166.72 (C=O, minor), 143.28 (CH$_{BImidazole}$), 131.72 (C$_{Ar}$), 130.76 (C$_{Ar}$), 126.94 (CH$_{Ar}$), 126.71 (CH$_{Ar}$), 124.46, 121.23, 118.00, 114.76 (q, J=322, CF$_3$), 113.96 (CH$_{Ar}$), 113.78 (CH$_{Ar}$), 62.78 (CH$_2$-O, minor), 62.13 (CH$_2$-O, major), 47.62 (CH$_2$-N), 46.95 (α-CH$_2$), 38.43 (-C-), 31.24 (ω-2), 28.58 (2), 28.47 (bulk-CH$_2$), 25.77 (β), 22.15 (ω-1), 21.07 (CH$_3$, major), 20.78 (CH$_3$, minor), 14.10 ((ω), minor), 13.94 ((ω), major); ^{19}F (336, MHz) δ ppm: −80.02; HRMS: m/z, [M^{+3}–2H]−3NTF$_2$$^-$ calcd. for C$_{56}$H$_{79}$N$_6$O$_6$$^{5+}$: 931.6061, found: 931.6028; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9201.

5.4.24 Synthesis of Tris-((*N*-decyl-benzimidazoliumyl-acetayloxy)methyl)ethane bis(trifluoromethylsulphonyl)amide (11e)

This compound was prepared analogously to **10a** using tris-((*N*-decyl-benzimidazol-iumyl-acetayloxy)methyl)ethane chloride **9e** (1.12 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 90% yield (1.67 g). Molecular Formula: $C_{68}H_{93}F_{18}N_9O_{18}S_6$; Mol. Wt.: 1858.88; FTIR (cm^{-1}): 3130 (C-H)$_{Ar}$, 2949, 2924, 2848 (C-H)$_{Aliph}$, 1749 (C=O), 1620 (C=N), 1566 1485, 1457 (C=C)$_{Ar}$, 1367, 1223 (C-F), 1360, 1165 (O=S=O), 1218, 1199 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.54 (s, 3H, C-H$_{BImidazole}$, minor), 9.48 (s, 3H, C-H$_{BImidazole}$, minor), 9.42 (s, 3H, C-H$_{BImidazole}$, major), 8.02-7.82 (m, 6H, CH$_{Ar}$), 7.73-7.55 (m, 6H, CH$_{Ar}$), 5.51 (s, 6H, O-CH$_2$, minor), 5.50 (s, 6H, O-CH$_2$, minor), 5.48 (s, 6H, O-CH$_2$, major), 4.57 (t, *J*=7.20, 6H, α-CH$_2$, major), 4.50 (t, *J*=7.20, 6H, α-CH$_2$, minor), 4.21 (s, 6H, N-CH$_2$, major), 4.19 (s, 6H, N-CH$_2$, minor), 4.17 (s, 6H, N-CH$_2$, minor), 2.04- 1.94 (m, 6H, β-CH$_2$), 1.27 (bs, 42H, bulk-CH$_2$), 1.04 (s, 3H, CH$_3$, major), 1.02 (s, 3H, CH$_3$, minor), 0.88 (t, 9H, *J*=6.78, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.66 (C=O, major), 167.57 (C=O, minor), 144.05 (CH$_{BImidazole}$), 133.31 (C$_{Ar}$), 132.57 (C$_{Ar}$), 128.78 (CH$_{Ar}$), 128.60 (CH$_{Ar}$), 126.17, 122.95, 119.73, 116.51 (q, *J*=320, CF$_3$), 114.79 (2) (CH$_{Ar}$), 68.07 (CH$_2$-O, minor), 67.85 (CH$_2$-O, major), 46.69 (CH$_2$-N), 41.89 (α-CH$_2$, minor), 41.70 (α-CH$_2$, major), 40.50 (-C-), 33.17 (ω-2), 30.72, 30.65, 30.54, 30.25 (2) (bulk-CH$_2$), 27.58 (β), 23.85 (ω-1), 17.07 (CH$_3$, minor), 16.97 (CH$_3$, major), 14.58 (ω); ^{19}F (336, MHz) δ ppm: –80.06; HRMS: m/z, [M^{+3}–2H]−3NTF$_2$$^-$ calcd. for $C_{62}H_{91}N_6O_6^{5+}$: 1015.7000, found: 1015.6977; m/z, [NTF$_2$]$^-$ calcd. for $C_2F_6NO_4S_2^-$: 279.9173, found: 279.9175.

5.4.25 Synthesis of Tris-((*N*-dodecyl-benzimidazoliumyl-acetayloxy)methyl)ethane bis(trifluoromethylsulphonyl)amide (11f)

This compound was prepared analogously to **10a** using tris-((*N*-dodecyl-benzimidaz-oliumyl-acetayloxy)methyl)ethane chloride **9f** (1.21 g, 1.0 mmol) and Lithium bis-

(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 96% yield (1.87 g). Molecular Formula: C$_{74}$H$_{105}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1943.04 ; FTIR (cm^{-1}): 3127 (C-H)$_{Ar}$, 2965 (C-H)$_{Aliph}$, 1750 (C=O), 1622 (C=N), 1565, 1485, 1448 (C=C)$_{Ar}$, 1362, 1222 (C-F), 1358, 1167 (O=S=O), 1210, 1170 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.72 (s, 3H, C-H$_{BImidazole}$, minor), 9.69 (s, 3H, C-H$_{BImidazole}$, minor), 9.65 (s, 3H, C-H$_{BImidazole}$, major), 8.00-7.91 (m, 6H, C-H$_{BImidazole}$), 7.71-7.54 (m, 6H, C-H$_{Ar}$, major), 7.40-7.31 (m, 6H, C-H$_{Ar}$, minor), 5.60 (s, 6H, O-CH$_2$, major), 5.57 (s, 6H, O-CH$_2$, minor), 4.53 (t, J=7.07, 6H, α-CH$_2$, major), 4.34 (t, J=7.07, 6H, α-CH$_2$, minor), 4.19 (s, 6H, N-CH$_2$, major), 4.16 (s, 6H, N-CH$_2$, minor), 1.98-1.92 (m, 6H, β-CH$_2$), 1.24 (bs, 54H, bulk-CH$_2$), 1.03 (s, 3H, CH$_3$, minor), 1.00 (s, 3H, CH$_3$, minor), 0.97 (s, 3H, CH$_3$, major), 0.86 (t, J=7.25, 9H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 166.89 (C=O), 143.75 (CH$_{BImidazole}$, major), 143.51(CH$_{BImidazole}$, minor), 133.10 (C$_{BImidazole}$), 130.92 (C$_{BImidazole}$), 128.08 (CH$_{Ar}$), 127.12 (CH$_{Ar}$), 126.36, 123.14, 119.92, 116.71 (q, J=320, CF$_3$), 114.81 (CH$_{Ar}$), 114.76 (CH$_{Ar}$), 68.37 (CH$_2$-O, minor), 68.24 (CH$_2$-O, major), 45.70 (CH$_2$-N), 40.18 (α-CH$_2$), 39.34 (-C-), 31.65 (ω-2), 29.66 (2), 29.32, 29.22, 29.03, 28.93, 28.86 (bulk-CH$_2$), 25.82 (β), 22.53 (ω-1), 16.23 (CH$_3$, minor), 16.03 (CH$_3$, major), 14.19 (ω); ^{19}F (336, MHz) δ ppm: −80.20; HRMS: m/z, [M^{+3}–2H]−3NTF$_2$$^-$ calcd. for C$_{68}$H$_{103}$N$_6$O$_6$$^{5+}$: 1099.7939, found: 1099.7977; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9225.

5.4.26 Synthesis of Tris-((*N*-benzyl-benzimidazoliumyl-acetayloxy)methyl)ethane bis(trifluoromethylsulphonyl)amide (11g)

This compound was prepared analogously to **10a** using tris-((*N*-benzyl-benzimidaz-oliumyl-acetayloxy)methyl)ethane chloride **9g** (0.97 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.0 g, 3.5 mmol) to provide a clear viscous hygroscopic liquid at room temperature in 96% yield (1.63 g). Molecular Formula: C$_{59}$H$_{51}$F$_{18}$N$_9$O$_{18}$S$_6$; Mol. Wt.: 1708.45; FTIR (cm^{-1}): 3127 (C-H)$_{Ar}$, 2965 (C-H)$_{Aliph}$,

1750 (C=O), 1622 (C=N), 1565, 1485, 1448 (C=C)$_{Ar}$, 1362, 1222 (C-F), 1358, 1167 (O=S=O), 1210, 1170 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.44 (s, 3H, C-H$_{BImidazole}$, major), 10.30 (s, 3H, C-H$_{BImidazole}$, minor), 10.13 (s, 3H, C-H$_{BImidazole}$, minor), 8.12-8.00 (m, 6H, C-H$_{Ar}$), 7.61-7.53 (m, 12H, C-H$_{Ar}$), 7.39-7.22 (m, 9H, C-H$_{Ar}$), 5.92 (s, 6H, CH$_2$-Ar), 5.84 (s, 6H, O-CH$_2$, major), 5.79 (s, 6H, O-CH$_2$, minor), 4.04 (s, 6H, N-CH$_2$, major), 3.99 (s, 6H, N-CH$_2$, minor), 0.91 (s, 3H, CH$_3$, minor), 0.86 (s, 3H, CH$_3$, minor), 0.82 (s, 3H, CH$_3$, major); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 168.01 (C=O, major), 166.57 (C=O, minor), 143.48 (CH$_{BImidazole}$, major), 142.82 (CH$_{BImidazole}$, minor), 133.82 (-$\underline{C}_{Ar}$-CH$_2$-), 131.79 (C$_{BImidazole}$), 130.48 (C$_{BImidazole}$), 129.10 (2×CH$_{Ar}$), 128.87 (CH$_{Ar}$), 128.31 (2×CH$_{Ar}$), 126.98 (CH$_{BImidazole}$), 126.81 (CH$_{BImidazole}$), 124.37, 121.13, 117.90, 114.66 (q, J=322, CF$_3$), 114.06 (CH$_{BImidazole}$), 113.89 (CH$_{BImidazole}$), 63.33 (CH$_2$-O, major), 62.67 (CH$_2$-O, minor), 50.00 (CH$_2$-N), 47.72 (Ar-CH$_2$-, major), 47.61 (Ar-CH$_2$-, minor), 40.63 (-C-), 16.33 (CH$_3$, major), 16.08 (CH$_3$, minor); ^{19}F (336, MHz) δ ppm: –79.95; HRMS: m/z, [M^{+3}–2H]−3NTF$_2^-$ calcd. for C$_{53}$H$_{49}$N$_6$O$_6$$^{5+}$:865.3714, found: 865.3750; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2^-$: 279.9173, found: 279.9214.

5.4.27 Liquid crystal behaviour

Liquid crystalline properties of compounds **8b-f** and **9b-f** were investigated thermotropically and lyotropically. Optical polarising microscopy (Olympus BH-2 OPM equipped with Mettler FF82 hot stage and Mettler FP80 Central Processor) was used to identify the optical textures and the transition temperatures. A contact penetration technique (Rendall, Tiddy, & Trevethan, 1983) was applied in lyotropic investigation. It was carried out at room temperature with water and 1-undecanol as polar and nonpolar solvents, respectively. The images were recorded at 50× magnification.

5.4.28 Air-water interface tension

The surface tensions were measured using KSV Sigma 702 tensiometer at 25 ± 0.5 ºC. The measurements were based DuNouy ring method in five replications with a standard deviation of less than 0.1 mN m^{-1}. The critical micelle concentration, CMC, was obtained from surface tension against logarithmic concentration plot through the intersection of two regression lines, where one of them is concentration dependent. Solutions were prepared using deionized water which was also filtered through 0.25 μm pore membrane producing 71.96 ± 0.09 mN m^{-1}, 0.9996 ± 0.0002 g mL^{-1} and 1.0 ± 0.1 μS cm^{-1} values for surface tension, density and conductivity, respectively.

5.4.29 Krafft point (T_K)

The determination of Krafft temperature, (T_k), was applied through slow heating of 1 % (w/v) aqueous solution of ILs surfactant in water bath. It was heated on an IKA hot plate stirrer equipped with temperature controller IKA ETS-D4 at 5 ºC. min^{-1} over the range 10 ºC to 50 ºC. The changes of transparency was optically monitored to observe the temperature of clear solution formed (Piasecki & Piłakowska-Pietras, 2007).

5.4.30 Closed Bottle Test

The biodegradability of synthesized ILs (*i.e.* **8b-g** and **9b-g**) was evaluated using Closed-Bottle test (OECD 301D) standard protocols (Sigua *et al.*, 2005). The analysis was based on biochemical oxygen demand (BOD) due to IL microbial degradation as reported (Coleman & Gathergood, 2010). The BOD values were derived from the quantified respirometric dissolved oxygen (DO) in a culture containing either IL or sodium *n*-dodecyl sulphate; SDS as a reference sample. The DO was measured using CyberScan dissolve oxygen meter $DO300$ (Eutech Instruments; The Netherlands).

All samples were prepared in capped Scotch bottles, each containing 100 ml of sample solution at 100 mg/L concentration of IL or reference sample in distilled water.

Each sample bottle was inoculated with 1 mL of microbial effluent collected from a wastewater treatment plant. The samples were prepared in three different groups of 3 replicates per each sample. Group 1 contained both inoculum and the IL samples, Group 2 contained only the inoculum (test blank) and Group 3 contained the inoculum and the reference sample (SDS). The solutions were incubated in the dark at 25 ±1°C for 28 days under continuous shaking (200 rpm), and the DO values were recorded after every 48 hours. Since the majority of biodegradation changes are only noticed within the first 16 days period of time, the results for 10 and 16 days were considered.

The BOD values were calculated based on observed DO using Equation (5.1) as reported in literature (Massardier-Nageotte, Pestre, Cruard-Pradet, & Bayard, 2006),

$$BOD = \frac{DO_o - DO_t}{\varphi} \qquad (5.1)$$

where DO_o is initial dissolved oxygen and DO_t is the dissolved oxygen at time t. While φ is fractional oxygen volume defined as the ratio of the experimental DO volume to theoretical DO volume that obtained from reference sample.

Further, the percentage biodegradation was calculated according to Equation (5.2) as following (Coleman & Gathergood, 2010):

$$Biodegradation = \frac{BOD}{ThOD\left(\frac{mg\ O_2}{mg\ sample\ weight}\right)} \times 100 \qquad (5.2)$$

where $ThOD$ represents the theoretical oxygen demand; the amount of oxygen consumed by the microorganisms in sample corrected for the uptake of O_2 by the blank inoculums (Coleman & Gathergood, 2010).

CHAPTER 6: TETERAKIS- IMIDAZOLIUM AND BENZIMIDAZOLIUM IONIC LIQUIDS: A NEW CLASS OF BIODEGRADABLE SURFACTANTS

Nassir N. Al-Mohammed, Rusnah Syahila Duali Hussen, Tammar Hussein Ali, Yatimah Alias and Zanariah Abdullah, *RSC Advances***, Manuscript published February-19-2015**
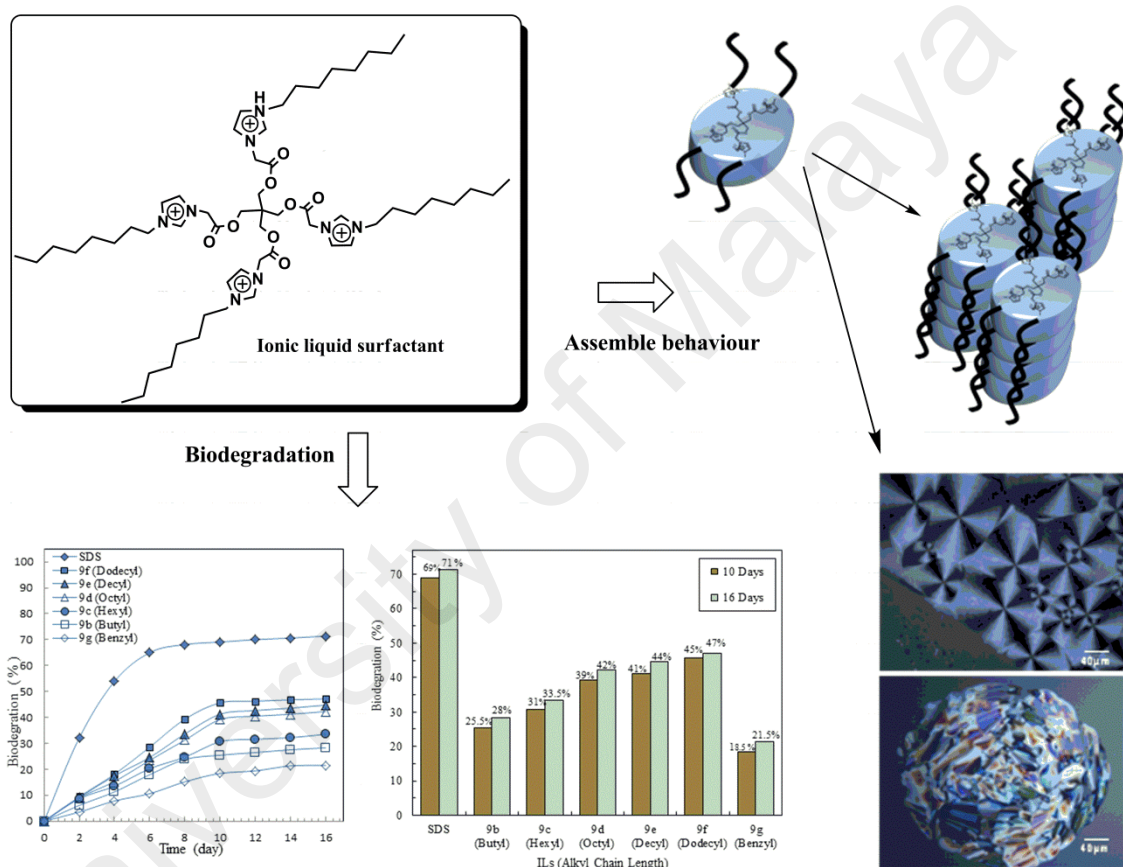
Novel tetrakis-imidazolium and benzimidazolium ILs containing tetra-ester groups with incorporated quadruple side chains were synthesized successfully as degradable surfactants of expected medicinal and industrial applications.

6.1 INTRODUCTION

Ionic liquids (ILs) are salts and entirely composed of ions: organic cation with delocalized charges associated with weakly coordinating anions. ILs as neoteric compounds have become increasingly classified as ''green'' solvents due to their negligible vapour pressure, non-flammability, recyclability, and potential solvation (Li *et al.*, 2013; Plechkova & Seddon, 2007; Rooney & Seddon, 2001; Sheldon, 2001; Sheldon, 2005). Generally, their chemical and physical properties can be tuned for a given application by varying both cationic and anionic components (Wasserscheid & Welton, 2007; Welton, 1999). Currently, due to the potential and present wide applications of ILs, a comprehensive evaluation of their environmental and hazardous effects is essential. Therefore, ILs estimation in the environment is considered as an important and active core for different studies related to toxicity (Docherty & Kulpa, 2005; Ferlin *et al.*, 2013; Hajfarajollah *et al.*, 2014; Kulacki & Lamberti, 2008; Latala *et al.*, 2010; Matsumoto, Mochiduki, & Kondo, 2004; Zhao, Liao, *et al.*, 2007), ecotoxicity (Matzke *et al.*, 2007; Petkovic *et al.*, 2011; Pretti *et al.*, 2009; Ventura, Gardas, Gonçalves, & Coutinho, 2011), bioaccumulation (Deng *et al.*, 2012; Pham, Cho, Jeon, *et al.*, 2008; Stolte *et al.*, 2008) and biodegradation (Docherty *et al.*, 2007; Harjani, Singer, *et al.*, 2009; Klein *et al.*, 2013; Steudte *et al.*, 2014). Although the low vapour pressure and highly chemical stability of ILs may reduce air pollution compared to the conventional organic solvents, many classes of ILs are water–soluble even those containing long hydrocarbon chains or with lipophilic anions. Moreover, as a result of their high stability in water, ILs may consider as persistent organic pollutants (POPs) in wastewaters. Thus, the determination of their potential environmental risk is of high priority.

Through designing linear alyklbenzenesulfonates and dialkyl quaternary compounds as biodegradable surfactants, Boethling (Boethling, 1994) emphasized the importance of

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designing biodegradable chemicals to reduce pollution at the source. Due to the structural similarity among many surfactants, like quaternary ammonium compounds, as well as ILs based on imidazolium cores, the factors improving the biodegradation of surfactants could apply to ILs. Towards biodegradation improvement, the structures design that is applied to ILs based on the surfactant preparation are: the presence of phenyl rings or linear hydrocarbon chains with ≥4 carbon atoms and the existence of esters or amides as hydrolysable groups (Boethling, 1996; Howard *et al.*, 1991). By achieving these factors relation to surfactant, rod-like molecules such as single-chain imidazole derivatives generated nematic (N) and bilayer smectic A (SmA) phases (Cheng *et al.*, 2010; Plechkova & Seddon, 2008). Columnar phase was generated due to the triple and quadruple-tail compounds with a tendency to form a wedge-shaped or disc-shaped molecule. Wedge-shaped molecules had an affinity to form higher-ordered molecular arrangements such as columnar (col) or cubic (cub) phases (Ichikawa *et al.*, 2012; Sander *et al.*, 2011). Generally, the higher-ordered phases were considered a good candidate for anisotropic ion conductor application (Axenov & Laschat, 2011). Moreover, compared to single-chain mono-ionic surfactants, the surface tension of multi-ionic head groups reduced upon increasing the number of the alkyl chains (*i.e.* double- or triple- chain amphiphiles) with enhancing interfacial properties (Okahara, Masuyama, Sumida, & Zhu, 1988; Zhu *et al.*, 1993). Further, more CH_3 groups were comparatively arranged to be on the outermost layer, which resulted in decreasing the surface energy (Zhao, Li, *et al.*, 2007).

Gathergood and co-workers used the structure design of biodegradable surfactants to improve the biodegradation of imidazolium ILs series containing incorporated alkyl side chain into functional ester or amide groups (Gathergood *et al.*, 2004; Gathergood & Scammells, 2002). The observed improvement was attributed to enzymatic hydrolysis susceptibility of the ester group compared to non-functional equivalent ILs: 1-butyl-3-

methylimidazolium tetrafluoroborate [bmim][BF$_4$] and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF$_6$]. Studies by Garcia *et al.* (2005); Harjani, Farrell, Garcia, Singer, and Scammells (2009); Harjani *et al.* (2008) of ILs series with and without ester groups, confirmed biodegradation improvement in the presence of an ester linkage. Further, Morrissey *et al.* (2009) supported the above previous studies that revealed an ester group is the favourite over an amide when investigated the biodegradability of synthesized ILs series containing a wide range of ether and poly ether esters. All of these studies as well as a study carried out by Gathergood *et al.* (2006) proved that octylsulphate counter ions had the highest biodegradation.

The biodegradability of ILs has been evaluated using a number of standard methods. The methods were developed by the Organisation for Economic Co-operation and Development (OECD) as series of guidelines (OECD; OECD; OECD). They included: DOC Die-Away Test (OECD 301 A), CO$_2$ Evolution-modified Sturm Test (OECD 301 B), CO$_2$ Headspace Test (ISO 14593), and Closed Bottle Test (OECD 301 D). Generally, the most used frequently methods are modified Sturm and Closed Bottle Tests (OECD 301 B and D, respectively). Based on sufficient interval measurements, different parameters such as dissolved organic carbon (DOC), carbon dioxide production and oxygen uptake can be used as criteria for ILs degradation. In current study, Closed Bottle Tests (OECD 301 D) was used to assess the biodegradability of the prepared ILs. The ILs were added to an aerobic aqueous medium inoculated with wastewater microorganisms. The depletion of dissolved molecular oxygen was measured for defined period (28 days) and presented as a percentage of the theoretical maximum. The evaluated ILs with 60% or higher biodegradation level are considered as ''readily biodegradable'' which was defined as compounds rapidly and completely decomposing or reaching ultimate biodegradability in aquatic environments under aerobic conditions and stringent test.

In continuation to the synthesis of new multi-cationic ILs (Al-Mohammed, Duali Hussen, Alias, *et al.*, 2015), current study involves design and synthesis of novel series of tetrakis-imidazolium and tetrakis-benzimidazolium ILs. The molecule design of ILs emphasized on increasing hydrolysable sites; multi-ester groups and incorporated alkyl or phenyl side chains with an expected higher-ordered phase (*e.g.* columnar phase) as targeted materials. Towards quadruple side chains of degradable IL surfactants with highly expected medical and industrial applications, the biodegradation of the synthesized halogen ILs were evaluated using the 'Closed Bottle Test' (OECD 301 D). The presence of ester groups with longer alkyl chains of the tetrakis-imidazolium ILs showed a more significant degradability comparing to mono and tri-cationic ILs. Further unique studies of their phase behaviours and surface properties were contributed. The effects of anions on phase behaviour and biodegradation are beyond the scope of this study.

6.2 RESULTS AND DISCUSSION

6.2.1 Synthesis

Tetrakis-imidazolium and tetrakis-benzimidazolium ILs were prepared based on a certain strategy in the previous tris-cationic study by the same authors (Al-Mohammed, Duali Hussen, Alias, *et al.*, 2015). With regard to the high purity and excellent yield of ILs, alpha position halides to carbonyl compound represented excellent starting materials. Therefore, the esterification of pentaerythritol (2,2-bis(hydroxymethyl)-1,3-propanediol) in net chloroacetyl chloride was a perfect process to obtain active tetra-ester halides compound. The syntheses of incorporated alkyl (or phenyl) side chains IL series containing tetra ester groups depended on the production of a variety of alkyl (or phenyl) imidazoles and benzimidazoles. Alkylation of the obtained alkyl imidazoles and benzimidazoles with active tetra-ester halide in acetonitrile at 50 – 60 °C provided the quantitative yields of certain tetra-cationic IL as shown in Figure 6.1. The production of

alkyl (or phenyl) imidazole and benzimidazole by treating imidazole or benzimidazole solids with alkyl halides under basic conditions has been described in our previous work (Al-Mohammed, Duali Hussen, Alias, *et al.*, 2015).

A good yield of NTf$_2$-ILs was produced by counter-ions exchange in an aqueous solution of chloride anions and bis(trifluoromethane)sulphonimide lithium salt. Clear liquid samples of hydrophobic ILs were obtained after simple extraction with ethyl acetate and the organic layer evaporation under reduced pressure. The purity of the NTf$_2$-ILs was confirmed by ^{13}C and ^{9}F-NMR. All the chloride ILs prepared in the current work are viscous syrup or semi-solid to solid with melting points below 100 °C and have been set as benchmark to determine their classification as ILs (Seddon, 2003) (as summarized in Table 6.1).
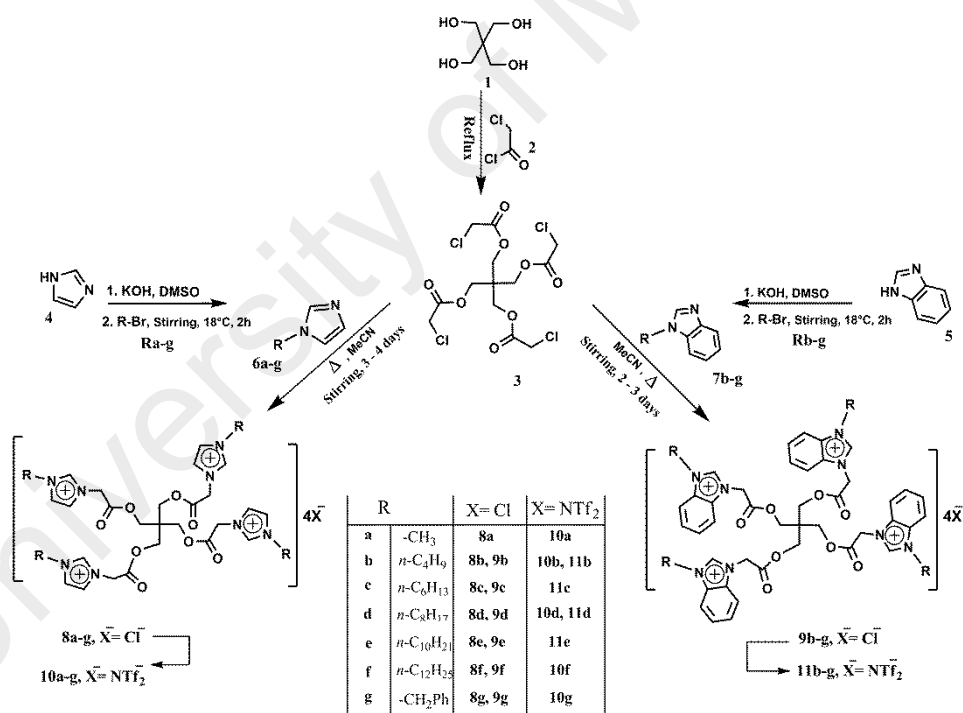
Figure 6.1: Synthesis of tetrakis-imidazolium and tetrakis-benzimidazolium ILs

Table 6.1: Structural and synthetic details of tetrakis-imidazolium and tetrakis-benzimidazolium ILs

IL	Cations	Alkyl chains	Counter ions	Status[c]	Mol. wt	m.p (°C)	Yield (%)
8a	Im[a]	CH$_3$	Cl$^-$	Solid	770.49	52-54	98
8b	Im[a]	n-C$_4$H$_9$	Cl$^-$	Semi-solid	938.81	-	97
8c	Im[a]	n-C$_6$H$_{13}$	Cl$^-$	Syrup	1051.02	-	98
8d	Im[a]	n-C$_8$H$_{17}$	Cl$^-$	Syrup	1163.23	-	98
8e	Im[a]	n-C$_{10}$H$_{21}$	Cl$^-$	Syrup	1275.45	-	99
8f	Im[a]	n-C$_{12}$H$_{25}$	Cl$^-$	Syrup	1387.66	-	99
8g	Im[a]	-CH$_2$-Ph	Cl$^-$	Semi-solid	1074.87	-	94
9b	BIm[b]	n-C$_4$H$_9$	Cl$^-$	Solid	1139.04	48-50	99
9c	BIm[b]	n-C$_6$H$_{13}$	Cl$^-$	Solid	1251.26	54-56	98
9d	BIm[b]	n-C$_8$H$_{17}$	Cl$^-$	Syrup	1363.47	-	99
9e	BIm[b]	n-C$_{10}$H$_{21}$	Cl$^-$	Syrup	1475.68	-	97
9f	BIm[b]	n-C$_{12}$H$_{25}$	Cl$^-$	Syrup	1587.89	-	98
9g	BIm[b]	-CH$_2$-Ph	Cl$^-$	Solid	1275.10	50-52	99
10a	Im[a]	-CH$_3$	NTf$_2^-$	liquid	1329.98	-	91
10b	Im[a]	n-C$_4$H$_9$	NTf$_2^-$	liquid	1456.22	-	91
10d	Im[a]	n-C$_8$H$_{17}$	NTf$_2^-$	liquid	1540.38	-	95
10f	Im[a]	n-C$_{12}$H$_{25}$	NTf$_2^-$	liquid	1708.70	-	93
10g	Im[a]	-CH$_2$-Ph	NTf$_2^-$	liquid	1558.27	-	96
11b	BIm[b]	n-C$_4$H$_9$	NTf$_2^-$	liquid	1606.39	-	94
11c	BIm[b]	n-C$_6$H$_{13}$	NTf$_2^-$	liquid	1774.71	-	98
11d	BIm[b]	n-C$_8$H$_{17}$	NTf$_2^-$	liquid	1858.88	-	98
11e	BIm[b]	n-C$_{10}$H$_{21}$	NTf$_2^-$	liquid	2454.45	-	98

[a] Imidazolium

[b] Benzimidazolium

[c] at room temperature

6.2.2 Liquid crystalline behaviour

Crystalline properties of compounds **8b-f** and **9b-f** were investigated thermotropically and lyotropically using optical polarizing microscope equipped with heating stage. In pure form, all the compounds of tetrakis-imidazolium series exist as liquid crystals with clearing point ranging from 94–176 °C. In general, ILs of tetrakis-imidazolium showed clearing points higher than tetrakis-benzimidazolium for the same side chains, where this behaviour was attributed to the presence of benzene ring in the cationic head. The phase is identified as columnar phase based on the fan-shaped texture characteristic, where Figure. 6.2 showed the columnar phase of **8c** and **8f** compounds. Clearer textures were observed on cooling from isotropic, and occasionally, the phase

formation was very slow. Compounds with chains length ≥ C10 carbons showed smectic A (SmA) phases as illustrated in Figure 6.3 for compound **8e**. Based on the chemical structures of tetrakis-imidazolium ILs, columnar phase is more favourable where the molecules had arranged as a rigid core at the centre and alkyl chains at the periphery, as illustrated in Figure. 6.4. Quadruple-chain crystals of tetra-coordinated silver (I) cation showed a similar columnar mesomorphism structure when incorporated with TfO⁻ as a counter ion. The coordination of these IL crystals based on disubstituted chelating of 2,2'-bipyridines ligands was considered as drive force for assembly beside the ionic bonds (Pucci *et al.*, 2005).
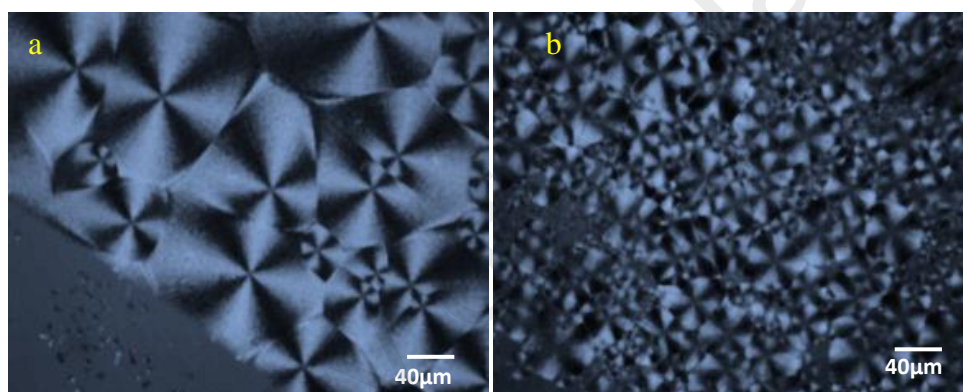
Figure 6.2: Polarized optical microscopic image of columnar phase of (a) **8c** and (b) **8f** at 10× magnification.
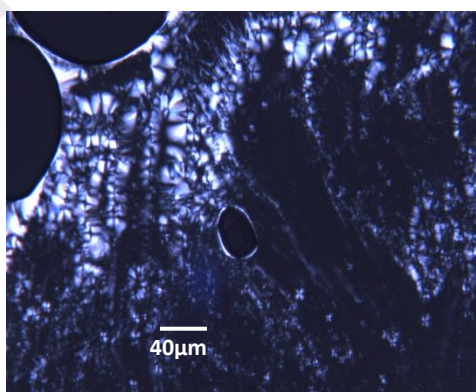
Figure 6.3: Polarized optical microscopic image of smectic A texture for compound **8e** at 10× magnification.
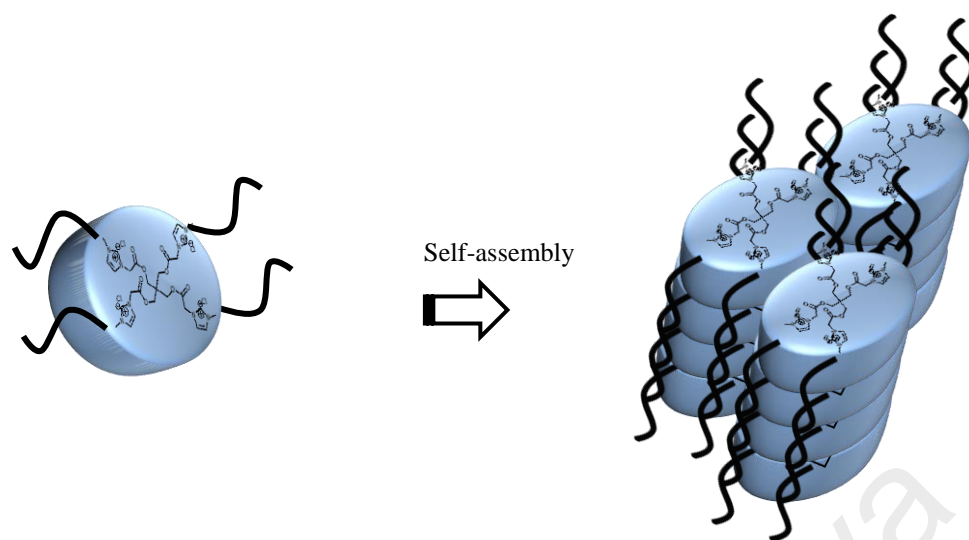
Figure 6.4: Discotic shape molecular assembly in columnar.

In contact with water as polar solvent, all the series of tetrakis-imidazolium ILs were very soluble, whereas at certain concentration gradients, they demonstrated a typical texture of lyotropic hexagonal phase, H_1. With higher water content, compounds **8d** and **8e** showed an extra mesomorphism; clearly discontinuous cubic phase, I_1 due to slow dissolving. An example for compound **8e** is illustrated in Figure 6.5.
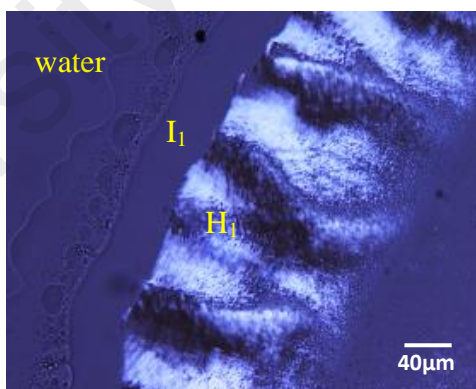
Figure 6.5: Polarized optical microscopic image of **8e** contacted with water at $10\times$ magnification.

Furthermore, for contact with non-polar solvent; 1-undecanol, the slow dissolving of tetrakis-imidazolium ILs showed similar behaviour to polar solvent, producing an inverted hexagonal phase. Figure 6.6 (a) and (b) illustrated assembly behaviour for compound **8d** after a few minutes' and 12 hours contact with 1-undecanol, respectively.
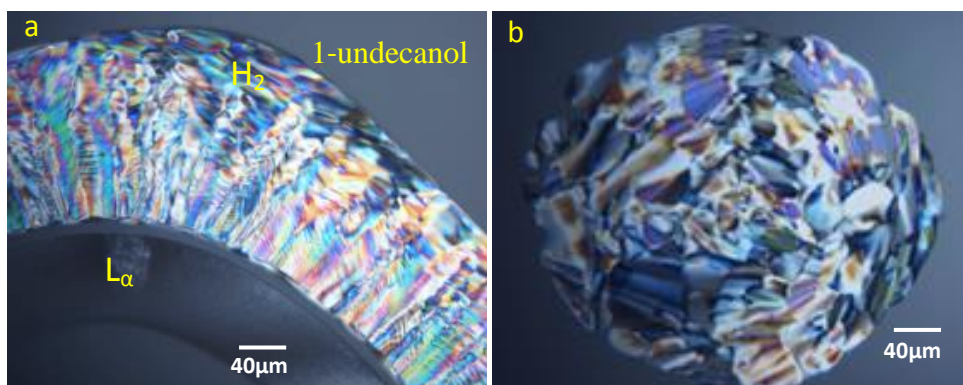
Figure 6.6: Columnar phase of **8d** (a) after a few minutes' contacted with 1-undecanol, and (b) overnight at 10× magnification.

In the absence of a solvent, there was no birefringent exhibition in tetrakis-bezimidazolium series ILs, where it appeared as glassy state and dark with no reflection. While in contact with water, compounds of the shorter chains length, such as **9c** were very soluble. Compound **9d** was soluble with hexagonal phase as shown in Figure 6.7 (a). Longer chains such as **9e** and **9f** are crystallized in water and the appearance of the crystals is shown in Figure 6.7 (b) and (c), respectively.
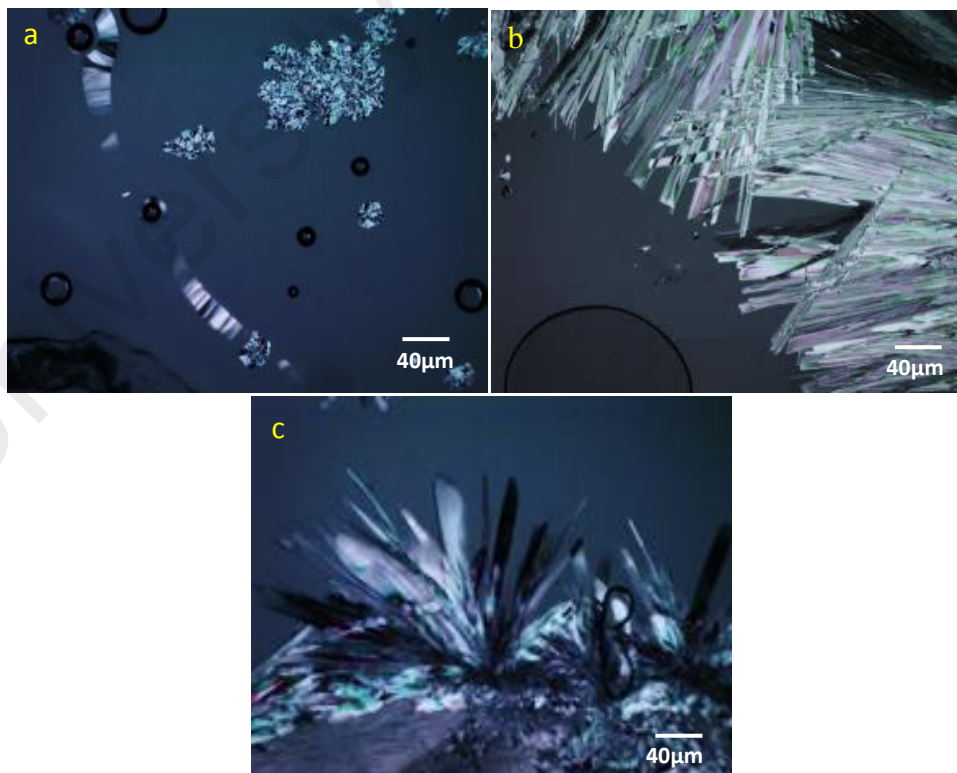
Figure 6.7: Columnar phase at 10× magnification (a) **9d** showing hexagonal phase after a few minutes' contacted with water, (b) **9e** and (c) **9f** showing crystallization in water.

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Lastly, all tetrakis-bezimidazolium ILs reacted similarly to the non-polar solvent which was an inverted hexagon as shown in Figure 6.8 (a) and (b) for compounds **9c** and **9f**, respectively. The phase behaviour results of the synthesized ILs are summarized in Table 6.2.
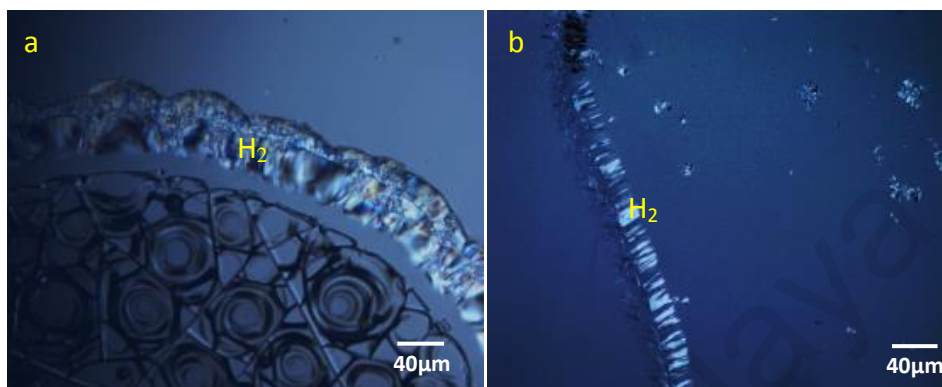
Figure 6.8: Inverted hexagonal phase of (a) **9c** and (b) **9f** at 10× magnification.

Table 6.2: Phase behaviours of synthesized tetrakis-imidazolium and bezimidazolium ILs as a function of alkyl chain length.

IL	Number of carbon atoms in side chains	Clearing point (°C)	Phase behaviour		
			In pure[b]	In water[c]	In 1-undecanol[d]
8b	4	ND[a]	-	-	-
8c	6	ND[a]	Columnar	L_1	L_2, H_2, V_2
8d	8	ND[a]	Columnar	L_1, I_1, H_1	L_2, H_2
8e	10	176	Columnar	L_1, I_1, H_1	L_2, H_2
8f	12	172	Columnar	L_1, H_1	L_2
9b	4	107	-	-	-
9c	6	159	Glassy state	L_1, H_1	H_2, V_2
9d	8	120	Glassy state	H_1	H_2
9e	10	94	Glassy state	Crystallize	H_2
9f	12	117	Glassy state	Crystallize	H_2

[a] not detected
[b] is absence of solvent
[c] is contact with water
[d] is contact with 1-undecanol

6.2.3 Air-water interface behaviour

All IL surfactants exhibited Krafft points below 10 °C, where based on their Krafft temperature, the air-water interface was preferred at room temperature. The behaviour of surfactants was investigated by systematic surface tension measurements over a wide

range of concentrations at 25 °C. Data regarding the micellar assembly for the surfactants are tabulated in Table 6.3.

Table 6.3: CMC values and surface tension properties of ILs/water systems.

IL	Carbon atoms in side-chain	CMC (mM)	γ_{cmc} (mN/m)	T_K (°C)
8b	4	-	-	-
8c	6	39.17	29	<10
8d	8	6.28	31	<10
8e	10	1.03	29	<10
8f	12	0.14	34	<10
8g	Benzyl	-	-	-
9b	4	-	-	-
9c	6	33.07	34	<10
9d	8	5.83	29	<10
9e	10	0.63	31	<10
9f	12	0.07	32	<10
9g	Benzyl	-	-	-

The surface tension above the CMC values was found to be in the range of 29– 34 mNm^{-1}, a similar trend to mono-imidazolium ILs containing ester groups was indicated in literature (Ahmad, Patial, Kaur, & Kaur, 2014). Compounds **9e** and **9f** were crystallized in a high concentration of 10 mM, which was above their CMC values.

Comparing tetrakis-imidazolium and tetrakis-benzimidazolium IL surfactants revealed a decrease in CMC upon the introduction of benzimidazole, as seen in the values for **9c**, **9d**, **9e** and **9f**. This reduction of the CMC could be attributed to the presence of an aromatic ring that considerably increased the surfactant hydrophobicity, whereas the CMC at surface tension itself was not greatly affected.

The current CMC values of tetra-IL surfactants were considerably lower than the corresponding tris-IL surfactants values as reported in a previous work by the same authors (Al-Mohammed, Duali Hussen, Alias, *et al.*, 2015). Precisely, the introduction of one additional hydrocarbon alkyl-chain to the amphiphilic antipodes affected the CMC values, while the minimum surface tension (γ_{min}) had a less effect. These interface

behaviour results were found to be in line with literature (Okahara *et al.*, 1988; Zhao, Li *, et al.*, 2007).

6.2.4 Biodegradation results

The biodegradation results of synthesized ILs, **8b-g** and **9b-g**, are presented in Figure 6.9 and Figure 6.10, respectively. Generally, ILs bearing imidazolium cations exhibited higher degradation percentage compared to those with benzimidazolium, besides, the existence of long linear alkyl side chain improved the biodegradation. For example, compound **8f** with a dodecyl side chain had a degradation percentage of 56%, while **9f** revealed a reduction in IL degradation to 47% due to the cationic part changing to benzimidazolium with the same side chain. This lower degradation in benzimidazolium ILs was attributed to the existence of aromatic rings fusion in benzimidazolium that improved the molecular stability against microbial degradation (Coleman & Gathergood, 2010).

In fact, the presence of ester group in ILs enhanced the biodegradation by providing a hydrolytic site for enzymatic attack (Atefi *et al.*, 2009; Docherty *et al.*, 2007; Gore & Gathergood, 2013; Hajipour & Rafiee, 2009). Therefore, tetra-ester groups of the current ILs improved the degradation to produce the corresponding primary alcohol that is metabolized *via* fatty acid β-oxidation (Gathergood *et al.*, 2004; Scott & Jones, 2000). Compared to the 34% degradation of imidazolium ILs as indicated in literature with mono-ester groups (Gathergood *et al.*, 2004), tetrakis-imidazolium and benzimidazolium ILs in the current study demonstrated significant biodegradation enhancement.
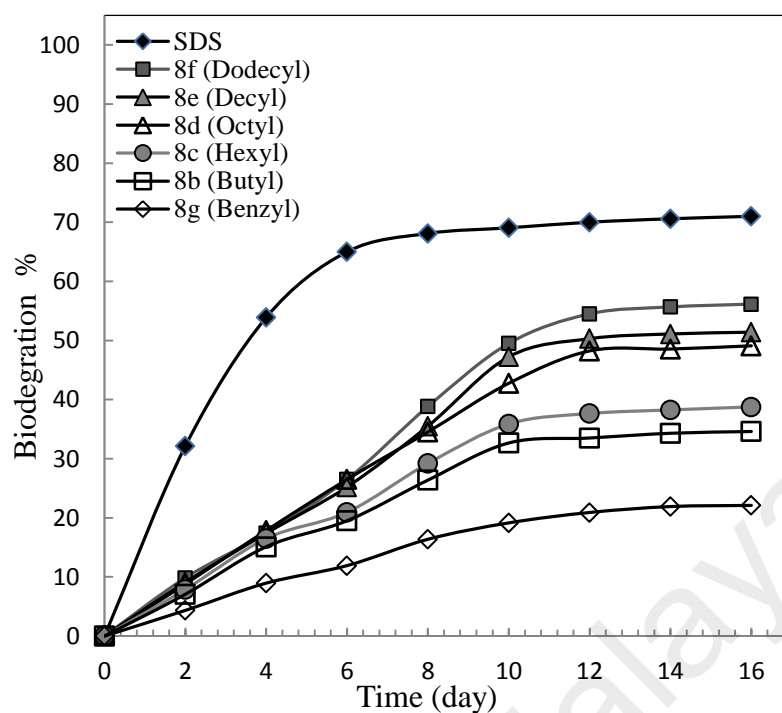
Figure 6.9: Biodegradation curves of tetrakis-imidazolium ILs series using closed-bottle test.
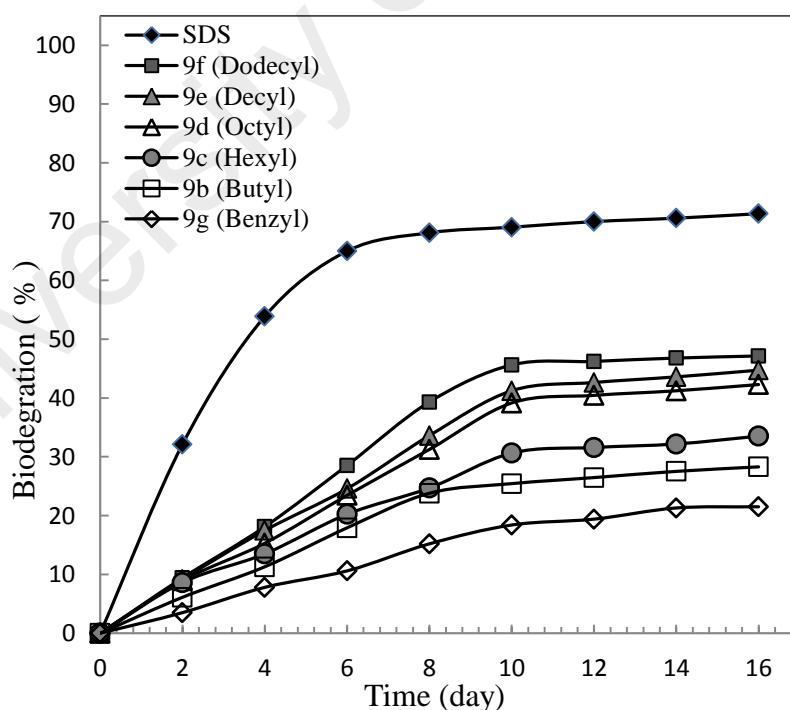
Figure 6.10: Biodegradation curves of tetrakis-benzimidazolium ILs series using closed-bottle test.

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The influence of side chains on IL degradation was evaluated as shown in Table 6.4. Compound **8f** was observed to have a higher percentage of degradation, at 56%, attributed to the presence of a dodecyl side chain (Gore & Gathergood, 2013). In contrast, lower percentage degradation, from 22 to 21.5%, was observed in ILs carrying aryl side chains in compounds **8g** and **9g**, respectively, as shown in Figure 6.11 and Figure 6.12. The results obtained from biodegradation evaluation studies are summarized in Table 6.4.

Table 6.4: Biodegradation results of synthesized tetrakis-imidazolium and bezimidazolium ILs as a function of alkyl chain length.

IL	Carbon atoms in side-chain	Biodegradation (%)	
		10 day	*16 day*
8b	4	33	35
8c	6	36	39
8d	8	44	49
8e	10	47	51.5
8f	12	49.5	53
8g	Benzyl	19	22
9b	4	25.5	28
9c	6	31	33.5
9d	8	39	42
9e	10	41	44
9f	12	45	47
9g	Benzyl	18	21.5

The longer alkyl side chains in the ILs provided a non-obstructed site for microbial digestion, and indicated a distinction in the degradation (Docherty *et al.*, 2007). Moreover, a linear alkyl side chain of mono-cationic ILs with length ≥4 carbons atoms was documented (Garcia *et al.*, 2005; Gathergood *et al.*, 2004; Gore & Gathergood, 2013; Harjani *et al.*, 2008; Harjani, Singer*, et al.*, 2009; Ventura *et al.*, 2013) as an important factor in designing biodegradable compounds owing to their ability to provide potential sites for oxygenases attack.

Furthermore, two potential effects of the longer alkyl side chain could improve IL degradation (Docherty *et al.*, 2007) by either i) eliminating any structural hindrance between the cationic ring and potential binding site, thereby allowing the IL backbone

to become more easily accessible to bacteria enzymatic digestion, or ii) the hydrophobicity of the ILs due to the longer alkyl side chain could influence its toxicity. Increasing the toxicity of the ILs could kill most of the microbes in the sludge, and allow capable metabolizing species to grow faster and proliferate.
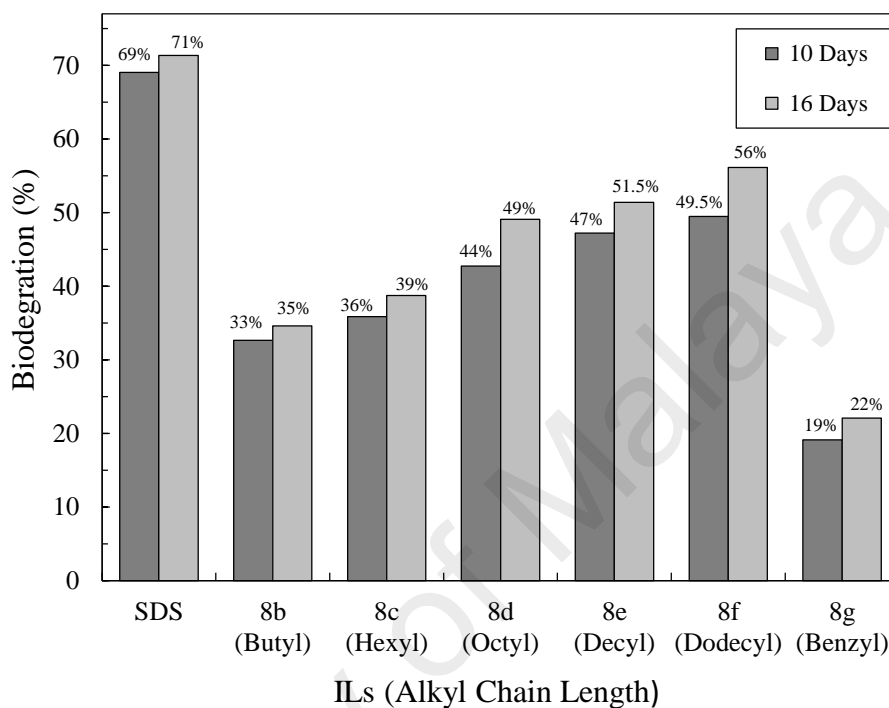
Figure 6.11: Biodegradation of tetrakis-imidazolium ILs series as a function of aliphatic or aromatic side chain on 10 and 16 days.
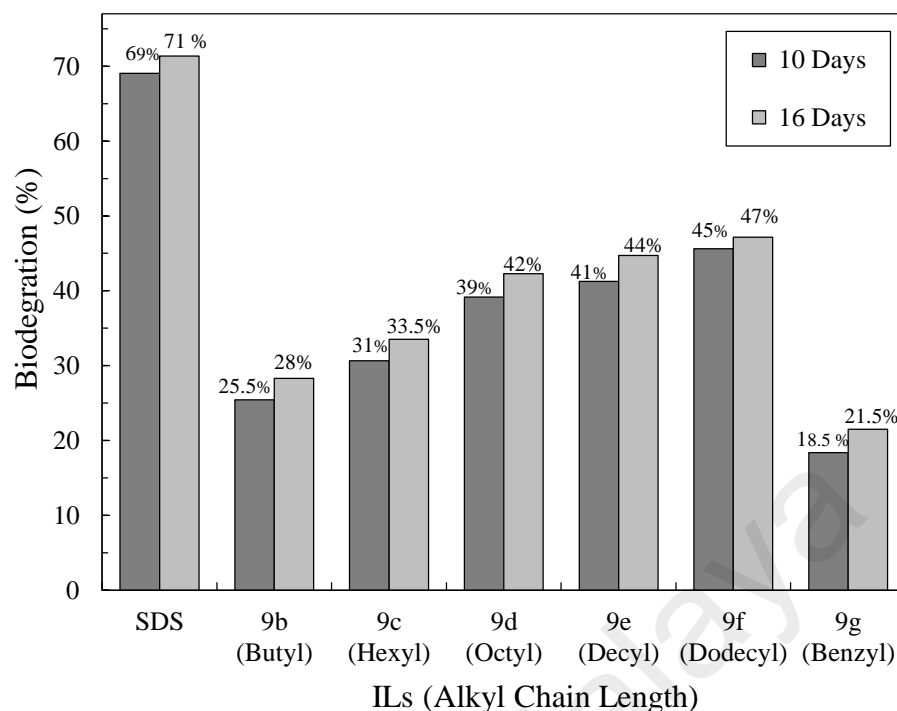
Figure 6.12: Biodegradation of tetrakis-benzimidazolium ILs series as a function of aliphatic or aromatic side chain on 10 and 16 days.

In the current study, each biodegradation test is considered as completed after 16 days duration out of 28 days, due to obtaining plateau for the last three measurements of the degradation curve (Coleman & Gathergood, 2010; Gathergood & Scammells, 2002). After this period, the results revealed negligible changes in consumption of biological oxygen demand (BOD) for all the tested ILs, as shown in Figures 6.9 and 6.10. Moreover, in comparison to tris-cationic ILs (Al-Mohammed, Duali Hussen, Alias, *et al.*, 2015) and with reference to the standard SDS samples, the tetra-cationic ILs achieved complete degradation with minor differences in biodegradation values in the 10 to 16 days' readings, as illustrated Figures 6.11 and 6.12. Finally, the tested tetrakis-imidazolium and tetrakis-benzimidazolium ILs exhibited a significant level of biodegradation. The data indicated that compounds; **8d**, **8e**, **8f** and **9f** were on the border of the 60% readily biodegradation pass level (Docherty *et al.*, 2007; Gathergood & Scammells, 2002) at 49.5%, 51.5%, 56% and 47%, respectively after 16 days' evaluation.

6.3 CONCLUSIONS

Two series of tetrakis-imidazolium and benzimidazolium ILs with incorporated alkyl or phenyl side chains containing tetra-ester groups and chloride as anions were successfully synthesized. Metathesis of these anions to NTf_2 at room temperature was tuned from viscous syrup, semi-solid or solid forms to clear liquids in excellent yield and purity. Both series of chloride anions were able to form a columnar/hexagonal phase. Unlike benzimidazolium, the imidazolium series readily existed as a columnar liquid crystal with the ability to be formed in polar or non-polar solvents at certain concentration. Tetrakis-imidazolium ILs displayed significant increase in phase behaviour properties and biodegradation compared to benzimidazolium ILs and effectively reduced the water surface tension to a range of 29– 34 mN m^{-1}. Comparing to tris-cationic ILs that were reported in a previous study by current authors (Al-Mohammed, Duali Hussen, Alias, *et al.*, 2015), the biodegradation and assembly behaviour for synthesized tetrakis-imidazolium and benzimidazolium ILs were highly enhanced by increasing the ILs hydrophobicity. Precisely, hexyl to dodecyl in the hydrocarbon chains for both imidazolium and bezimidazolium ILs presented phase behaviours in contact with solvents whether polar or non-polar in addition to further textures for tetrakis-imidazolium ILs appeared in pure form.

In the synthesized tetra-cationic ILs, the presence of ester groups as an enzymatic hydrolysis sites with long linear alkyl chains or phenyl rings that improved the biodegradation of surfactants were successfully applied to ILs. In addition, octyl, decyl, and dodecyl as side chains presented very close values to the pass level (60%) of the readily biodegradation Closed Bottle Test results. Nonetheless, owing to potential beneficial effects of biodegradable octylsulphate ($C_8H_{17}OSO_3$) as anion(Gathergood *et al.*, 2006), readily degradable of the current tetrakis-imidazolium and tetrakis-benzimidazolium ILs 60-70% degradation within the test period (Docherty *et al.*, 2007)

could be achieved in future study. As a matter of fact, since the fluorine compounds effectively reduce water surface tension (Aliaga, Santos, & Baldelli, 2007), a more detailed study of the current tetra-cationic incorporated with NTf_2 as counter-ions is in progress to explore more effective surfactant ILs.

6.4 EXPERIMENTAL

1-Methylimidazole and 1-butylimidazol were purchased from Aldrich and distilled before used to remove impurities detrimental to all ILs prepared. The syntheses of alkyl imidazole and benzimidazole; 1-Hexylimidazole, 1-octylimidazole, 1-decylimi- dazole, 1-dodecylimidazole, 1-benzylimidazol, 1-butylbenzimidazole, 1-hexylbenzimi- dazole, 1-octylbenzimidazole, 1-decylbenzimidazole, 1-dodecylbenzimidazole, and 1-benzyl-benzimidazole were described and reported in a previous work (Al-Mohammed, Duali Hussen, Alias, *et al.*, 2015). All ILs were kept in a fridge (5 °C) and freezer (–18 °C) for further evaluation of their properties. General grade solvents and reagents were purchased from commercial suppliers and used without further purification. Melting points were determined on an optical polarizing microscope with hot stage and were uncorrected. The IR spectra were obtained with a Perkin Elmer 400 Fourier Transform Infrared (FTIR) spectrometer. The ^{1}H and ^{13}C-NMR spectra were recorded on Jeol Lambda and ECA- DELTA as well as Bruker spectrometers at 400 MHz. High-resolution mass spectra were recorded on Agilent Technologies 6530 Accurate Q-TOF LC–MS system, applying DMSO /MeOH eluents for ILs sample compounds while Agilent 5975 system for EI/MS (NUS, Singapore) was applied for the rest of the compounds. Thin layer chromatography was carried out on pre-coated silica gel plates (0.25 mm, 20 × 20 cm, 60F254, E. Merck).

6.4.1 Procedure for Synthesis of compound 3

This compound was prepared according to the modification applied on a procedure described in literature (Ropponen *et al.*, 2004). Pentaerythritol (2,2-Bis(hydroxymethyl)

-1,3-propanediol) 1 (10 g, 73.4 mmol) was dissolved and refluxed with a minimum amount of chloroacetyl chloride 2 for 3–5 hours or until all HCl gas was liberated (pursue by wet litmus paper). The reaction mixture was evaporated in vacuo until the excess of acid chloride was removed. The crude product was purified by co-evaporation with toluene (4–5 times) to produce a white solid. Re-crystallization from dry acetonitrile gave compound 3 as white flakes.

Tetrakis-((2-chloro-acetayloxy)methyl)methane (3): White colour flakes; yield: 30.8 g (95%); m.p 92-94 °C. Molecular Formula: $C_{13}H_{16}Cl_4O_8$; mol. wt.: 442.07; FTIR (cm^{-1}): 2970, 2875 (C-H)$_{Aliph}$, 1749 (C=O), 1185, 1160 (O-C), 789 (C-Cl); ^{1}H-NMR (400 MHz, CDCl$_3$) δ: 4.24 (s, 8H, CH$_2$-Cl), 4.06 (s, 8H, CH$_2$-O); ^{13}C-NMR (100 MHz, CDCl$_3$) δ ppm: 166.89 (C=O), 63.49 (CH$_2$-O), 42.73 (-C-), 40.69 (CH$_2$-Cl); EIMS (m/z): 439.9 (8%)(M$^{+\bullet}$), 364.9 (22%), 289.0 (30%), 213.0 (57%), 137.0 (73%), 90.9 (87%), 47.0 (100%).

6.4.2 Synthesis of Tetrakis-((*N*-methyl-imidazoliumyl-acetayloxy)methyl)methane chloride (8a)

A solution of 1-methylimidazole (1.41 g, 1.37 mL, 17.2 mmol) in acetonitrile anhydrous (5mL) was added drop-wise to a stirred solution of tetrakis-((2-chloro-acetayloxy)methyl)methane (compound **3**) (1.9g, 4.30 mmol) in acetonitrile anhydrous (15 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred vigorously for 3 h and refluxed at 50–55 °C for 3–4 days. The acetonitrile top layer was decanted and the IL washed with diethyl ether (3 × 10 mL), then residual solvent removed *in vacuo*. The product was dried at (40 °C, 0.01 mmHg) for 48 h to give a white hygroscopic solid (m.p 52–54°C) in 98% yield (3.25 g). Molecular Formula: $C_{29}H_{40}Cl_4N_8O_8$; mol. wt.: 770.49; FTIR (cm^{-1}): 3068 (C-H)$_{Ar}$, 2977, 2930 (C-H)$_{Aliph}$, 1744 (C=O), 1603 (C=N), 1575, 1511 (C=C)$_{Ar}$, 1215, 1162 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d₆*) δ ppm: 7.66 (s, 4H, C-H$_{Imidazole}$, minor), 7.62 (s, 4H, C-H$_{Imidazole}$, major), 7.15 (bt~s, 4H,C-H$_{Imidazole}$, minor), 7.11 (bt~s, 4H, C-H$_{Imidazole}$, major), 6.94

(bt~s, 4H, C-H$_{Imidazole}$, minor), 6.90 (bt~s, 4H, C-H$_{Imidazole}$, major), 3.77 (s, 16H, O-CH$_2$, N-CH$_2$, minor), 3.73 (s, 16H, O-CH$_2$, N-CH$_2$, major), 3.67 (s, 12H, N-CH$_3$, minor), 3.63 (s, 12H, N-CH$_3$, major); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 168.09 (C=O, minor), 166.67 (C=O, major), 137.87 (CH$_{Imidazole}$, major), 137.66 (CH$_{Imidazole}$, minor), 123.74 (CH$_{Imidazole}$), 123.28 (CH$_{Imidazole}$, major), 123.19 (CH$_{Imidazole}$, minor), 63.86 (CH$_2$-O, minor), 63.28 (CH$_2$-O, major), 49.71 (CH$_2$-N, minor), 49.51 (CH$_2$-N, major), 41.60 (-C-), 35.97 (CH$_3$-N, major), 35.89 (CH$_3$-N, minor); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for C$_{29}$H$_{37}$N$_8$O$_8$$^{7+}$: 625.2734, found: 625.2767.

6.4.3 Synthesis of Tetrakis-((*N*-butyl-imidazoliumyl-acetayloxy)methyl)methane chloride (8b)

This compound was prepared analogously to **8a** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-butylimidazole (2.14 g, 2.26 mL, 17.2 mmol) to give a white hygroscopic semi-solid in 97% yield (3.91 g). Molecular Formula: C$_{41}$H$_{64}$Cl$_4$N$_8$O$_8$; mol. wt.: 938.81; FTIR (cm^{-1}): 3060 (C-H)$_{Ar}$, 2959, 2932, 2865 (C-H)$_{Aliph}$, 1750 (C=O), 1644 (C=N), 1564, 1465 (C=C)$_{Ar}$, 1195, 1160 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.57 (bt~s, 4H, C-H$_{Imidazole}$, major), 9.52 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.45 (bt~s, 4H, C-H$_{Imidazole}$, minor), 7.91 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, major), 7.86 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, major), 7.76 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, minor), 7.69 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, minor), 5.47 (s, 8H, O-CH$_2$, major), 5.44 (s, 8H, O-CH$_2$, minor), 5.39 (s, 8H, O-CH$_2$, minor), 4.25 (t, J= 7.25 Hz, 8H, α-CH$_2$, major), 4.20 (s, 8H, N-CH$_2$, major), 4.11 (s, 8H, N-CH$_2$, minor), 3.98 (t, J= 7.25 Hz, 8H, α-CH$_2$, minor), 1.81-1.74 (m, 8H, β-CH$_2$, major), 1.72-1.64 (m, 8H, β-CH$_2$, minor), 1.30-1.18 (m, 8H, (ω-1)-CH$_2$), 0.89 (t, J =7.25 Hz, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 166.72 (C=O), 137.41 (CH$_{Imidazole}$), 123.96 (CH$_{Imidazole}$), 122.12 (CH$_{Imidazole}$), 63.42 (CH$_2$-O), 49.68 (CH$_2$-N, minor), 49.58 (CH$_2$-N, major), 48.73 (α-CH$_2$), 41.38 (-C-), 31.37 (ω-2), 18.78 (ω-1), 13.31 (ω); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for C$_{41}$H$_{61}$N$_8$O$_8$$^{7+}$: 793.4612, found: 793.4655.

6.4.4 Synthesis of Tetrakis-((*N*-hexyl-imidazoliumyl-acetayloxy)methyl)methane chloride (8c)

This compound was prepared analogously to **8a** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-hexylimidazole (**6c**) (2.62 g, 17.2 mmol) to give a viscous hygroscopic syrup in 98% yield (4.43 g). Molecular Formula: $C_{49}H_{80}Cl_4N_8O_8$; mol. wt.: 1051.02; FTIR (cm^{-1}): 3060 (C-H)$_{Ar}$, 2956, 2929, 2859 (C-H)$_{Aliph}$, 1751 (C=O), 1641 (C=N), 1564, 1463 (C=C)$_{Ar}$, 1195, 1165 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.68 (bt~s, 4H, C-H$_{Imidazole}$, major), 9.56 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.42 (bt~s, 4H, C-H$_{Imidazole}$, minor), 7.97 (t, *J* =1.95 Hz, 4H, C-H$_{Imidazole}$, major), 7.90 (t, *J* =1.95 Hz, 4H,C-H$_{Imidazole}$, minor), 7.88 (t, *J* =1.95 Hz, 4H, Hz, C-H$_{Imidazole}$, major), 7.82 (t, *J* =1.95 Hz, 4H, C-H$_{Imidazole}$, minor), 5.53 (s, 8H, O-CH$_2$, major), 5.47 (s, 8H, O-CH$_2$, minor), 5.40 (s, 8H, O-CH$_2$, minor), 4.25 (t, *J*= 7.32 Hz, 8H, α-CH$_2$), 4.19 (s, 8H, N-CH$_2$, major), 4.16 (s, 8H, N-CH$_2$, minor), 4.14 (bs, 8H, N-CH$_2$, minor), 1.82-1.75 (m, 8H, β-CH$_2$), 1.25 (bs, 24H, bulk-CH$_2$), 0.85 (t, 12H, *J* =6.83 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 168.13 (C=O, major), 166.72 (C=O, minor), 137.36 (CH$_{Imidazole}$, minor), 137.25 (CH$_{Imidazole}$, major), 123.95 (CH$_{Imidazole}$), 122.09 (CH$_{Imidazole}$, minor), 121.98 (CH$_{Imidazole}$, major), 64.87 (CH$_2$-O, major), 64.32 (CH$_2$-O, minor), 49.80 (CH$_2$-N), 49.01 (α-CH$_2$, minor), 48.94 (α-CH$_2$, major), 48.85 (α-CH$_2$, minor), 41.60 (-C-), 30.55 (ω-2), 29.38 (bulk-CH$_2$), 25.16 (β-CH$_2$, minor), 25.11 (β-CH$_2$, major), 21.94 (ω-1), 13.88 (ω); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for $C_{49}H_{77}N_8O_8{}^{7+}$: 905.5864, found: 905.5960.

6.4.5 Synthesis of Tetrakis-((*N*-octyl-imidazoliumyl-acetayloxy)methyl)methane chloride (8d)

This compound was prepared analogously to **8a** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-octylimidazole (**6d**) (3.10 g, 17.2 mmol) to give a viscous hygroscopic syrup in 98% yield (4.90 g). Molecular Formula: $C_{57}H_{96}Cl_4N_8O_8$; mol. wt.: 1163.23; FTIR (cm^{-1}): 3063 (C-H)$_{Ar}$, 2955, 2925,

2855 (C-H)$_{Aliph}$, 1750 (C=O), 1619 (C=N), 1563, 1463 (C=C)$_{Ar}$, 1202, 1166 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.72 (bt~s, 4H, C-H$_{Imidazole}$, major), 9.61 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.48 (bt~s, 4H, C-H$_{Imidazole}$, minor), 7.99 (t, 4H, J =1.81 Hz, C-H$_{Imidazole}$, major), 7.94 (t , 4H, J =1.81 Hz, C-H$_{Imidazole}$, minor), 7.93 (t , 4H, J =1.81 Hz, C-H$_{Imidazole}$, minor), 7.89 (t, 4H, J =1.81 Hz, C-H$_{Imidazole}$, major), 7.83 (t , 4H, J =1.81 Hz, C-H$_{Imidazole}$, minor), 5. 54 (s, 8H, O-CH$_2$, major), 5.48 (s, 8H, O-CH$_2$, minor), 5.47 (s, 8H, O-CH$_2$, minor), 4.27 (t, J= 7.70 Hz, 8H,α-CH$_2$), 4.18 (bs, 6H, N-CH$_2$, major), 4.09 (s, 8H, N-CH$_2$, minor), 1.82-1.75 (m, 8H, β-CH$_2$), 1.23 (bs, 40H, bulk-CH$_2$), 0.84 (t, J =6.80 Hz, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 168.13 (C=O, minor), 166.72 (C=O, major), 137.45 (CH$_{Imidazole}$, major), 137.22 (CH$_{Imidazole}$, minor), 123.94 (CH$_{Imidazole}$), 122.04 (CH$_{Imidazole}$, major), 121.96 (CH$_{Imidazole}$, minor), 63.86 (CH$_2$-O, minor), 63.41 (CH$_2$-O, major), 49.78 (CH$_2$-N, minor), 49.59 (CH$_2$-N, major), 48.96 (α-CH$_2$), 41.52 (-C-), 31.20 (ω-2), 29.45, 28.55, 28.37 (bulk-CH$_2$), 25.52 (β-CH$_2$), 22.10 (ω-1), 13. 98 (ω); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for C$_{57}$H$_{93}$N$_8$O$_8$$^{7+}$: 1017.7116, found: 1017.7160.

6.4.6 Synthesis of Tetrakis-((*N*-decyl-imidazoliumyl-acetayloxy)methyl)methane chloride (8e)

This compound was prepared analogously to **8a** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-decylimidazole (**6e**) (3.58 g, 17.2 mmol) to give a viscous hygroscopic syrup in 99% yield (5.43 g). Molecular Formula: C$_{65}$H$_{112}$Cl$_4$N$_8$O$_8$; mol. wt.: 1275.45; FTIR (cm^{-1}): 3130, 3065 (C-H)$_{Ar}$, 2950, 2925, 2857 (C-H)$_{Aliph}$, 1750 (C=O), 1623 (C=N), 1564, 1482 (C=C)$_{Ar}$, 1202, 1165 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 9.73 (bt~s, 4H, C-H$_{Imidazole}$, major), 9.62 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.48 (bt~s, 4H, C-H$_{Imidazole}$, minor), 7.99 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, major), 7.94 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, minor), 7.93 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, minor), 7.89 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, major), 7.85 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, minor), 7.83 (t, J =1.81 Hz, 4H, C-H$_{Imidazole}$, minor), 5.54 (s, 8H, O-

CH$_2$, major), 5.49 (s, 8H, O-CH$_2$, minor), 5.47 (s, 8H, O-CH$_2$, minor), 4.24 (t, J= 7.25 Hz, 8H, α-CH$_2$), 4.18 (s, 8H, N-CH$_2$, major), 4.09 (s, 8H, N-CH$_2$, minor), 1.82-1.75 (m, 6H, β-CH$_2$), 1.23 (bs, 56H, bulk-CH$_2$), 0.84 (t, 12H, J =6.80 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.10 (C=O, minor), 166.68 (C=O, major), 137.40 (CH$_{Imidazole}$, major), 137.20 (CH$_{Imidazole}$, minor), 123.90 (CH$_{Imidazole}$), 122.01 (CH$_{Imidazole}$), 63.85 (CH$_2$-O, minor), 63.31 (CH$_2$-O, major), 49.75 (CH$_2$-N, minor), 49.55 (CH$_2$-N, major), 48.94 (α-CH$_2$), 41.10 (-C-), 31.29 (ω-2), 29.42, 28.93, 28.87, 28.69, 28.39 (bulk-CH$_2$), 25.50 (β-CH$_2$), 22.11 (ω-1), 13.96 (ω); HRMS: m/z, [M^{+4}−3H]−4Cl$^-$ calcd. for C$_{65}$H$_{109}$N$_8$O$_8$$^{7+}$: 1129.8368, found: 1129.8284.

6.4.7 Synthesis of Tetrakis-((*N*-dodecyl-imidazoliumyl-acetayloxy)methyl)methane chloride (8f)

This compound was prepared analogously to **8a** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-dodecylimidazole (**6f**) (4.06 g, 17.2 mmol) to give a viscous hygroscopic syrup in 99% yield (5.90 g). Molecular Formula: C$_{73}$H$_{128}$Cl$_4$N$_8$O$_8$; mol. wt.: 1387.66; FTIR (cm^{-1}): 3128, 3062 (C-H)$_{Ar}$, 2957, 2924, 2855 (C-H)$_{Aliph}$, 1752 (C=O), 1625 (C=N), 1564, 1462 (C=C)$_{Ar}$, 1202, 1164 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.29 (bt~s, 4H, C-H$_{Imidazole}$, major), 9.24 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.19 (bt~s, 4H, C-H$_{Imidazole}$, minor), 7.76 (t, 1.95 Hz, 4H, C-H$_{Imidazole}$, major), 7.74 (t, 4H, J =1.95 Hz, C-H$_{Imidazole}$, major), 7.71 (t, 4H, J =1.95 Hz, C-H$_{Imidazole}$, minor), 7.66 (t, 4H, J =1.95 Hz, C-H$_{Imidazole}$, minor), 5.38 (s, 8H, O-CH$_2$, major), 5.36 (s, 8H, O-CH$_2$, minor), 5.34 (s, 8H, O-CH$_2$, minor), 4.35 (s, 8H, N-CH$_2$), 4.29 (t, J= 7.32 Hz, 8H, α-CH$_2$), 1.95-1.89 (m, 8H, β-CH$_2$), 1.29 (bs, 72H, bulk-CH$_2$), 0.89 (t, 12H, J =7.07 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 168.92 (C=O, minor), 167.79 (C=O, major), 138.87 (CH$_{Imidazole}$), 125.44 (CH$_{Imidazole}$), 123.58 (CH$_{Imidazole}$, major), 123.43 (CH$_{Imidazole}$, minor), 65.21 (CH$_2$-O, minor), 64.67 (CH$_2$-O, major), 51.27 (CH$_2$-N), 51.09 (α-CH$_2$, major), 50.93 (α-CH$_2$, minor), 43.70 (-C-), 33.19 (ω-2), 31.28, 30.88(2), 30.81, 30.70, 30.59, 30.26 (bulk-CH$_2$), 27.42 (β-CH$_2$, major),

27.32 (β-CH$_2$, minor), 23.86 (ω-1), 14.61 (ω); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for C$_{73}$H$_{125}$N$_8$O$_8$$^{7+}$: 1241.9620, found: 1241.9693.

6.4.8 Synthesis of Tetrakis-((*N*-benzyl-imidazoliumyl-acetayloxy)methyl)methane chloride (8g)

This compound was prepared analogously to **8a** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-benzylimidazole (**6g**) (2.72 g, 17.2 mmol) to give a pale-yellow hygroscopic semi-solid in 94% yield (4.34 g). Molecular Formula: C$_{53}$H$_{56}$Cl$_4$N$_8$O$_8$; mol. wt.: 1074.87; FTIR (cm^{-1}): 3132, 3032 (C-H)$_{Ar}$, 2930 (C-H)$_{Aliph}$, 1732 (C=O), 1612 (C=N), 1562, 1488 (C=C)$_{Ar}$, 1185, 1132 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.36 (s, 4H, C-H$_{Imidazole}$, major), 9.30 (s, 4H, C-H$_{Imidazole}$, minor), 9.25 (s, 4H, C-H$_{Imidazole}$, minor), 7.75 (t, *J* =1.81, 4H, C-H$_{Imidazole}$, major), 7.73 (t, *J* =1.81, 4H, C-H$_{Imidazole}$, minor), 7.72 (t, *J* =1.81, 4H, C-H$_{Imidazole}$, minor), 7.69 (t, *J* =1.81, 4H, C-H$_{Imidazole}$, minor), 7.68 (t, *J* =1.81, 4H, C-H$_{Imidazole}$, minor), 7.68 (t, *J* =1.81, 4H, C-H$_{Imidazole}$, minor), 7.67 (t, *J* =1.81, 4H, C-H$_{Imidazole}$, major), 7.46-7.20 (m, 20H, C-H$_{Ar}$), 5.48 (bs, 8H, Ar-CH$_2$-N), 5.37 (s, 8H, O-CH$_2$, major), 5.34 (s, 8H, O-CH$_2$, minor), 5.32 (s, 8H, O-CH$_2$, minor), 4.30 (d~t, 8H, N-CH$_2$, major), 4.27 (d~t, 8H, N-CH$_2$, minor); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 168.95 (C=O, minor), 167.74 (C=O, major), 166.82 (C=O, minor), 138.96 (CH$_{Imidazole}$), 135.26 (-C$_{Ar}$-CH$_2$-), 130.60 (2CH$_A$), 130.54 (CH$_{Ar}$) 129.90 (2CH$_{Ar}$), 125.70 (CH$_{Imidazole}$), 123.61 (CH$_{Imidazole}$, minor) 123.57 (CH$_{Imidazole}$, major), 64.51 (CH$_2$-O, major), 64. 27 (CH$_2$-O, minor), 64.04 (CH$_2$-O, minor), 54.40 (CH$_2$-N), 51.19 (Ar-CH$_2$-), 43.80 (-C-); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for C$_{53}$H$_{53}$N$_8$O$_8$$^{7+}$: 929.3986, found: 929.4052.

6.4.9 Synthesis of Tetrakis-((*N*-butyl-benzimidazoliumyl-acetayloxy)methyl)methane chloride (9b)

To a stirred solution of tetrakis-((2-chloro-acetayloxy)methyl)methane (compound **3**) (1.9g, 4.30 mmol) in acetonitrile anhydrous (15 mL), the solution of 1-butyl-benzimidazole (**7b**) (3.00 g, 17.2 mmol) in acetonitrile anhydrous (5 mL) was added drop-

wise at room temperature and under a nitrogen atmosphere. The reaction mixture was refluxed at 45–50 °C for 2–3 days, and then at room temperature for 5 h. The acetonitrile top layer was decanted and the IL was washed with diethyl ether (3 × 10 mL), then the residual solvent was evaporated under reduced pressure. The product was dried at (40 °C, 0.01 mmHg) for 72 h to give a white hygroscopic solid (m.p 48–50 °C) in 99% yield (4.85 g). Molecular Formula: $C_{57}H_{72}Cl_4N_8O_8$; mol. wt.: 1139.04; FTIR (cm^{-1}): 3133 (C-H)$_{Ar}$, 2950, 2935, 2859 (C-H)$_{Aliph}$, 1752(C=O), 1620(C=N), 1562, 1475, 1462 (C=C)$_{Ar}$, 1202, 1188 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.48 (s, 4H, C-H$_{BImidazole}$, major), 10.39 (s, 4H, C-H$_{BImidazole}$, minor), 10.27 (s, 4H, C-H$_{BImidazole}$ minor), 8.16 (dd, J=8.29, 8H, CH$_{Ar}$), 7.63 (dt, J=7.81, 8H, CH$_{Ar}$), 5.91 (s, 8H, O-CH$_2$, major), 5.86 (s, 8H, O-CH$_2$, minor), 5.80 (s, 8H, O-CH$_2$, minor), 4.58 (t, J=7.32, 8H, α-CH$_2$, major), 4.52 (t, J=7.32, 8H, α-CH$_2$, minor), 4.24 (s, 8H, N-CH$_2$, minor), 4.16 (s, 8H, N-CH$_2$, major), 4.10 (s, 8H, N-CH$_2$, minor), 1.91-1.83 (m, 8H, β-CH$_2$), 1.36- 1.27 (m, 8H, (ω-1)), 0.88 (t, 12H, J =7.32 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.05 (C=O, minor), 166.41 (C=O, major), 166.35 (C=O, minor), 143.39 (CH$_{BImidazole}$), 131.51 (C$_{Ar}$), 130.61 (C$_{Ar}$), 126.69 (CH$_{Ar}$), 126.66 (CH$_{Ar}$), 114.19 (CH$_{Ar}$), 113.74 (CH$_{Ar}$), 62.97 (CH$_2$-O), 47.64 (CH$_2$-N), 46.58 (α-CH$_2$, major), 46.40 ((α-CH$_2$), minor), 41.83 (-C-), 30.69 ((ω-2), minor), 30.48 ((ω-2), major), 19.00 (ω-1), 13.33 (ω); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for $C_{57}H_{69}N_8O_8{}^{7+}$: 993.5238, found: 993.5272.

6.4.10 Synthesis of Tetrakis-((*N*-hexyl-benzimidazoliumyl-acetayloxy)methyl)methane chloride (9c)

This compound was prepared analogously to **9b** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-hexyl-benzimidazole (**7c**) (3.48 g, 17.2 mmol) to give a white hygroscopic solid (m.p 54-56°C) in 98% yield (5.27 g). Molecular Formula: $C_{65}H_{88}Cl_4N_8O_8$; mol. wt.: 1251.26; FTIR (cm^{-1}): 3137 (C-H)$_{Ar}$, 2955, 2930, 2859 (C-H)$_{Aliph}$, 1752 (C=O), 1619(C=N), 1563, 1486, 1464 (C=C)$_{Ar}$, 1204,

1188 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.46 (s, 4H, C-H$_{BImidazole}$, major), 10.34 (s, 4H, C-H$_{BImidazole}$, minor), 8.15 (dd, J=8.29, 8H, CH$_{Ar}$), 7.64 (dt, J=7.81, 8H, CH$_{Ar}$), 5.90 (s, 8H, O-CH$_2$, major), 5.84 (s, 8H, O-CH$_2$, minor), 4.58 (t, J=7.32, 8H, α-CH$_2$), 4.22 (s, 8H, N-CH$_2$, minor), 4.19 (s, 8H, N-CH$_2$, major), 4.13 (s, 8H, N-CH$_2$, minor), 1.93-1.86 (m, 8H, β-CH$_2$), 1.26 (bs, 24H, bulk-CH$_2$), 0.83 (t, J=6.83, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.11 (C=O, minor), 166.48 (C=O, major), 143.99 (CH$_{BImidazole}$, minor),143.38 (CH$_{BImidazole}$, major), 131.52 (C$_{Ar}$), 130.63 (C$_{Ar}$), 126.71 (2 × CH$_{Ar}$), 114.22 (CH$_{Ar}$), 113.78 (CH$_{Ar}$), 63.00 (CH$_2$-O), 47.66 (CH$_2$-N), 46.82 (α-CH$_2$), 41.86 (-C-), 30.73 ((ω-2), minor), 30.61 ((ω-2), major), 28.53 (bulk-CH$_2$), 25.38 (β-CH$_2$), 21.93 (ω-1), 13.86 (ω); HRMS: m/z, [M^{+4}−3H]−4Cl$^-$ calcd. for C$_{65}$H$_{85}$N$_8$O$_8$$^{7+}$: 1105.6490, found: 1105.6538.

6.4.11 Synthesis of Tetrakis-((*N*-octyl-benzimidazoliumyl-acetayloxy)methyl)methane chloride (9d)

This compound was prepared analogously to **9b** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-octyl-benzimidazole (**7d**) (3.96 g, 17.2 mmol) to give a viscous hygroscopic syrup in 99% yield (5.80g). Molecular Formula: C$_{73}$H$_{104}$Cl$_4$N$_8$O$_8$; mol. wt.: 1363.47; FTIR (cm^{-1}): 3135 (C-H)$_{Ar}$, 2924, 2925, 2854 (C-H)$_{Aliph}$, 1751 (C=O), 1614 (C=N), 1562, 1486 1464 (C=C)$_{Ar}$, 1199 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.49 (s, 4H, C-H$_{BImidazole}$, major), 10.37 (s, 4H, C-H$_{BImidazole}$, minor), 8.16 (dd, J=8.05, 8H, CH$_{Ar}$), 7.63 (dt, J=7.81, 8H, CH$_{Ar}$), 5.91 (s, 8H, O-CH$_2$, major), 5.85 (s, 8H, O-CH$_2$, minor), 4.57 (t, J=7.32, 8H, α-CH$_2$), 4.23 (s, 8H, N-CH$_2$, minor), 4.17 (s, 8H, N-CH$_2$, major), 4.12 (s, 8H, N-CH$_2$, minor), 1.92- 1.85 (m, 8H, β-CH$_2$), 1.21 (bs, 40H, bulk-CH$_2$), 0.83 (t, 12H, J=6.34, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.84 (C=O, major), 166.51 (C=O, minor), 143.25 (CH$_{BImidazole}$), 131.57 (C$_{Ar}$), 130.63 (C$_{Ar}$), 126.79 (CH$_{Ar}$), 126.64 (CH$_{Ar}$, minor), 126.57 (CH$_{Ar}$, major), 114.04 (CH$_{Ar}$, minor), 113.88 (CH$_{Ar}$, major), 113.73 (CH$_{Ar}$), 65.07 (CH$_2$-O, major), 64.33 (CH$_2$-O, minor), 47.56 (CH$_2$-N), 46.77 (α-CH$_2$),

41.49 (-C-), 31.10 (ω-2), 28.53, 28.44, 28.33 (bulk-CH$_2$), 25.63 (β-CH$_2$), 22.00 (ω-1), 13.90 (ω); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for C$_{73}$H$_{101}$N$_8$O$_8$$^{7+}$: 1217.7742, found: 1217.7662.

6.4.12 Synthesis of Tetrakis-((*N*-decyl-benzimidazoliumyl-acetayloxy)methyl)methane chloride (9e)

This compound was prepared analogously to **9b** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-decyl-benzimidazole (**7e**) (4.44 g, 17.2 mmol) to give a viscous hygroscopic syrup in 97% yield (6.15g). Molecular Formula: C$_{81}$H$_{120}$Cl$_4$N$_8$O$_8$; mol. wt.: 1475.68; FTIR (cm^{-1}): 3134 (C-H)$_{Ar}$, 2962, 2923, 2854 (C-H)$_{Aliph}$, 1751 (C=O), 1622 (C=N), 1562 1486, 1463 (C=C)$_{Ar}$, 1203 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 10.50 (s, 4H, C-H$_{BImidazole}$, major), 10.38 (s, 4H, C-H$_{BImidazole}$, minor), 10.22 (s, 4H, C-H$_{BImidazole}$, minor), 8.16 (dd, *J*=8.29, 8H, CH$_{Ar}$), 7.63 (dt, *J*=7.81, 8H, CH$_{Ar}$), 5.91 (s, 8H, O-CH$_2$, major), 5.85 (s, 8H, O-CH$_2$, minor), 5.79 (s, 8H, O-CH$_2$, minor), 4.56 (t, *J*=7.05, 8H, α-CH$_2$, major), 4.49 (t, *J*=7.07, 8H, α-CH$_2$, minor), 4.17 (s, 8H, N-CH$_2$, major), 4.11 (s, 8H, N-CH$_2$, minor), 1.92- 1.85 (m, 8H, β-CH$_2$), 1.20 (bs, 56H, bulk-CH$_2$), 0.83 (t, 12H, *J*=6.10, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 167.07 (C=O, minor), 166.44 (C=O, major), 143.37 (CH$_{BImidazole}$, major), 142.25 (CH$_{BImidazole}$, minor), 131.50 (C$_{Ar}$), 130.61 (C$_{Ar}$), 126.67 (2 × CH$_{Ar}$), 114.19 (CH$_{Ar}$, major), 114.09 (CH$_{Ar}$, minor), 113.74 (CH$_{Ar}$), 63.00 (CH$_2$-O), 47.63 (CH$_2$-N), 46.79 (α-CH$_2$, major), 46.62 (α-CH$_2$, minor), 41.79 (-C-), 31.28 ((ω-2), major), 30.69 ((ω-2), minor), 28.91, 28.86, 28.67, 28.55, 28.45 (bulk-CH$_2$), 25.72 (β-CH$_2$), 22.08 (ω-1), 13.94 (ω).

6.4.13 Synthesis of Tetrakis-((*N*-dodecyl-benzimidazoliumyl-acetayloxy)methyl)-methane chloride (9f)

This compound was prepared analogously to **9b** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-dodecyl-benzimidazole (**7f**) (4.93 g, 17.2 mmol) to give a viscous hygroscopic syrup in 98% yield (6.69g).

Molecular Formula: $C_{89}H_{136}Cl_4N_8O_8$; mol. wt.: 1587.89; FTIR (cm^{-1}): 3134 (C-H)$_{Ar}$, 2955, 2925, 2855 (C-H)$_{Aliph}$, 1755 (C=O), 1620 (C=N), 1562, 1486, (C=C)$_{Ar}$, 1202 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.84 (s, 4H, C-H$_{BImidazole}$, major), 9.80 (s, 4H, C-H$_{BImidazole}$, minor), 9.75 (s, 4H, C-H$_{BImidazole}$, minor), 8.04-7.96 (m, 8H, CH$_{Ar}$), 7.73-7.54 (m, 8H, CH$_{Ar}$), 5.69 (s, 8H, O-CH$_2$, major), 5.67 (s, 8H, O-CH$_2$, minor), 5.65 (s, 8H, O-CH$_2$, minor), 4.61 (t, J=7.32, 8H, α-CH$_2$, minor), 4.55 (t, J=7.32, 8H, α-CH$_2$, major), 4.37 (s, 8H, N-CH$_2$, major), 4.34 (s, 8H, N-CH$_2$, minor), 4.25 (s, 8H, N-CH$_2$, minor), 2.06-1.98 (m, 8H, β-CH$_2$), 1.28 (bs, 72H, bulk-CH$_2$), 0.89 (t, J=7.07, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 168.84 (C=O, minor), 167.66 (C=O, major), 166.55 (C=O, minor), 144.15 (CH$_{BImidazole}$), 133.34 (C$_{Ar}$), 132.53 (C$_{Ar}$), 128.59 (CH$_{Ar}$), 128.52 (CH$_{Ar}$), 115.02 (CH$_{Ar}$), 114.76 (CH$_{Ar}$), 64.23 (CH$_2$-O, minor), 64.09 (CH$_2$-O, major), 63.71 (CH$_2$-O, minor), 48.44 (CH$_2$-N), 44.32 (α-CH$_2$), 41.78 (-C-), 33.18(ω-2), 30.87 (2), 30.80, 30.70, 30.59, 30.36, 30.32 (bulk-CH$_2$), 27.64 (β-CH$_2$), 23.86 (ω-1), 14.60 (ω).

6.4.14 Synthesis of Tetrakis-((*N*-benzyl-benzimidazoliumyl-acetayloxy)methyl)-methane chloride (9g)

This compound was prepared analogously to **9b** using tetrakis-((2-chloro-acetayloxy-)methyl)methane (compound **3**) (1.9 g, 4.30 mmol) and 1-benzyl-benzimidazole (**7g**) (3.58 g, 17.2 mmol) to give a pale yellow hygroscopic solid (m.p 50-52°C) in 99% yield (5.43g). Molecular Formula: $C_{69}H_{64}Cl_4N_8O_8$; mol. wt.: 1275.11; FTIR (cm^{-1}): 3132, 3032 (C-H)$_{Ar}$, 2935 (C-H)$_{Aliph}$, 1749 (C=O), 1614 (C=N), 1561, 1488, 1455 (C=C)$_{Ar}$, 1183 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.19 (s, 4H, C-H$_{BImidazole}$, minor), 10.03 (s, 4H, C-H$_{BImidazole}$, minor), 10.00 (s, 4H, C-H$_{BImidazole}$, major), 8.10-7.99 (m, 8H, C-H$_{Ar}$), 7.70-7.62 (m, 8H, C-H$_{Ar}$), 7.52-7.30 (m, 20H, C-H$_{Ar}$), 5.89 (s, 8H, CH$_2$-Ar), 5.88 (s, 8H, CH$_2$-Ar), 5.87 (s, 8H, CH$_2$-Ar), 5.66 (s, 8H, O-CH$_2$, minor), 5.56 (s, 8H, O-CH$_2$, minor), 5.53 (s, 8H, O-CH$_2$, major), 3.34 (s, 8H, N-CH$_2$, major), 3.27 (s, 8H, N-CH$_2$, minor); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 168.51 (C=O, minor), 167.84

(C=O, major), 166.58 (C=O, minor), 143.59 (CH$_{BImidazole}$), 133.93 (-C$_{Ar}$-CH$_2$-, major), 133.87 (-C$_{Ar}$-CH$_2$-, minor), 131.77 (C$_{BImidazole}$), 130.43 (C$_{BImidazole}$), 129.05 (2 × CH$_{Ar}$), 128.82 (CH$_{Ar}$, major), 128.68 (CH$_{Ar}$, minor), 128.34 (2 × CH$_{Ar}$), 126.94 (CH$_{BImidazole}$), 126.77 (CH$_{BImidazole}$), 114.29 (CH$_{BImidazole}$, minor), 114.07 (CH$_{BImidazole}$, major), 113.94 (CH$_{BImidazole}$), 60.69 (CH$_2$-O), 49.94 (CH$_2$-N, major), 49.06 (CH$_2$-N, minor), 47.82 (Ar-CH$_2$-), 41.58 (-C-); HRMS: m/z, [M^{+4}–3H]−4Cl$^-$ calcd. for C$_{69}$H$_{61}$N$_8$O$_8$$^{7+}$:1129.4612, found: 1129.4690.

6.4.15 Synthesis of Tetrakis-((*N*-methyl-imidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphoyl)amide (10a)

A flask was charged with tetrakis-((*N*-methyl-imidazoliumyl-acetayloxy)methyl)-methane chloride (**8a**) (0.77 g, 1.0 mmol) and de-ionized water (10 mL). Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) in de-ionized water (3 mL) was added in one portion and the suspension was stirred vigorously for 7 h at room temperature. The mixture was extracted with ethyl acetate (3×5mL) after stirring for 1h each time. The combined organic layers were evaporated on the rotary evaporator and under high vacuum for 8 h to remove the solvent and give a clear viscous hygroscopic liquid at room temperature in 91% yield (1.60 g). Molecular Formula: C$_{37}$H$_{40}$F$_{24}$N$_{12}$O$_{24}$S$_8$; mol. wt.: 1749.26; FTIR (cm^{-1}): 3082 (C-H)$_{Ar}$, 2976, 2922, 2856 (C-H)$_{Aliph}$, 1754 (C=O), 1652 (C=N), 1548, 1460 (C=C)$_{Ar}$, 1358, 1222 (C-F), 1365, 1157 (O=S=O), 1220, 1182(C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 8.90 (s, 4H, C-H$_{Imidazole}$, minor), 8.88 (s, 4H, C-H$_{Imidazole}$, minor), 8.86 (s, 4H, C-H$_{Imidazole}$, minor), 8.84 (s, 4H, C-H$_{Imidazole}$, major), 7.61 (t, 8H, *J*=1.81, Hz, C-H$_{Imidazole}$, major), 7.58 (t, 8H, *J*=1.81, Hz, C-H$_{Imidazole}$, minor), 7.56 (t, 8H, *J*=1.81, Hz, C-H$_{Imidazole}$, minor), 5.19 (s, 8H, O-CH$_2$, major), 5.18 (s, 8H, O-CH$_2$, minor), 5.17 (s, 8H, O-CH$_2$, minor), 4.33 (s, 8H, N-CH$_2$, major), 4.28 (s, 8H, N-CH$_2$, minor), 4.25 (s, 8H, N-CH$_2$, minor), 3.96 (s, 12H, N-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.72 (C=O, minor), 167.58 (C=O, major), 139.30 (CH$_{Imidazole}$), 126.12, 122.90, 119.69, 116.47 (q, *J*=320, CF$_3$),

125.18 (CH$_{Imidazole}$), 124.98 (CH$_{Imidazole}$, major), 124.94 (CH$_{Imidazole}$, minor), 65.07 (CH$_2$-O, minor), 64.29 (CH$_2$-O, major), 50.85 (CH$_2$-N), 44.27 (-C-), 36.89 (CH$_3$-N). ^{19}F (336, MHz) δ ppm: −80.06; HRMS: m/z, [M$^{\cdot+}$]−4NTF$_2^{-}$ calcd. for C$_{29}$H$_{37}$N$_8$O$_8^{7+}$: 625.2734, found: 625.2771; m/z, [NTF$_2$]$^{-}$ calcd. for C$_2$F$_6$NO$_4$S$_2^{-}$: 279.9173, found: 279.9177.

6.4.16 Synthesis of Tetrakis-((*N*-butyl-imidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphonyl)amide (10b)

This compound was prepared analogously to **10a** using tetrakis-((*N*-butyl-imidazol-iumyl-acetayloxy)methyl)methane chloride **8b** (0.94 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 91% yield (1.75 g). Molecular Formula: C$_{49}$H$_{64}$F$_{24}$N$_{12}$O$_{24}$S$_8$; mol. wt.: 1917.58; FTIR (cm^{-1}): 3064 (C-H)$_{Ar}$, 2951, 2935, 2855 (C-H)$_{Aliph}$, 1752 (C=O), 1648 (C=N), 1560, 1470 (C=C)$_{Ar}$, 1359, 1218 (C-F), 1357, 1152 (O=S=O), 1203, 1169 (C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 9.55 (bt~s, 4H, C-H$_{Imidazole}$, major), 9.49 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.42 (bt~s, 4H, C-H$_{Imidazole}$, minor), 7.90 (t, *J*=1.81, 4H, C-H$_{Imidazole}$, major), 7.85 (t, *J*=1.81, 4H, C-H$_{Imidazole}$, major), 7.73 (t, *J*=1.81, 4H, C-H$_{Imidazole}$, minor), 7.67 (t, 4H, *J*=1.81, C-H$_{Imidazole}$, minor), 5.45 (s, 8H, O-CH$_2$, major), 5.40 (s, 8H, O-CH$_2$, minor), 4.27 (t, *J*= 7.25 Hz, 8H, α-CH$_2$), 4.22 (s, 8H, N-CH$_2$), 3.99 (t, J= 7.25 Hz, 8H, α-CH$_2$, minor), 1.85-1.79 (m, 8H, β-CH$_2$), 1.28-1.19 (m, 8H, (ω-1)-CH$_2$), 0.90 (t, *J* =7.25 Hz, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 167.25 (C=O, minor), 166.83 (C=O, major), 137.62 (CH$_{Imidazole}$), 124.84 (CH$_{Imidazole}$), 123.75, 120.52 117.29, 114.06 (q, *J*=321, CF$_3$), 122.70 (CH$_{Imidazole}$), 64.66 (CH$_2$-O, minor), 64.17 (CH$_2$-O, major), 50.05 (CH$_2$-N), 49.01 (α-CH$_2$), 40.58 (-C-), 31.09 (ω-2), 19.12 (ω-1), 13.52 (ω). ^{19}F (336, MHz) δ ppm: −80.22; HRMS: m/z, [M^{+4}–3H]−4NTF$_2^{-}$ calcd. for C$_{41}$H$_{61}$N$_8$O$_8^{7+}$ 793.4612 found: 793.4644; m/z, [NTF$_2$]$^{-}$ calcd. for C$_2$F$_6$NO$_4$S$_2^{-}$: 279.9173, found: 279.9192.

6.4.17 Synthesis of Tetrakis-((*N*-octyl-imidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphonyl)amide (10d)

This compound was prepared analogously to **10a** using tetrakis-((*N*-octyl-imidazol-iumyl-acetayloxy) methyl)methane chloride **8d** (1.16 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 95% yield (2.03 g). Molecular Formula: C$_{65}$H$_{96}$F$_{24}$N$_{12}$O$_{24}$S$_8$; mol. wt.: 2142.00; FTIR (cm^{-1}): 3065 (C-H)$_{Ar}$, 2955, 2932, 2857 (C-H)$_{Aliph}$, 1751 (C=O), 1657 (C=N), 1560, 1467 (C=C)$_{Ar}$, 1353, 1220 (C-F), 1360, 1148 (O=S=O), 1199, 1177 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.06 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.02 (bt~s, 4H, C-H$_{Imidazole}$, minor), 8.99 (bt~s, 4H, C-H$_{Imidazole}$, major), 7.78 (t, *J*=1.81, 4H, C-H$_{Imidazole}$, major), 7.71 (t, 4H, *J*=1.81, C-H$_{Imidazole}$, minor), 7.66 (t, *J*=1.81, 4H, C-H$_{Imidazole}$, major), 7.62 (t, 4H, *J*=1.81, C-H$_{Imidazole}$, minor), 5.39 (s, 8H, O-CH$_2$, major), 5.28 (s, 8H, O-CH$_2$, minor), 4.30 (t, *J*= 7.25 Hz, 8H, α-CH$_2$), 4.25 (s, 8H, N-CH$_2$), 1.93-1.86 (m, 8H, β-CH$_2$), 1.30 (bs, 40H, bulk-CH$_2$), 0.90 (t, *J* =6.68 Hz, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.83 (C=O, minor), 167.71 (C=O, major), 138.67 (CH$_{Imidazole}$), 125.37, 122.14, 118.91, 115.69 (q, *J*=321, CF$_3$), 125.42 (CH$_{Imidazole}$), 123.64 (CH$_{Imidazole}$), 66.17 (CH$_2$-O, minor), 65.67 (CH$_2$-O, major), 52.35 (CH$_2$-N), 51.08 (α-CH$_2$), 42.52 (-C-), 33.09 (ω-2), 31.20, 30.42, 30.12 (bulk-CH$_2$), 27.33 (β), 23.82 (ω-1), 14.58 (ω). ^{19}F (336, MHz) δ ppm: −80.03; HRMS: m/z, [M^{+4}−3H]−4NTF$_2$$^-$ calcd. for C$_{57}$H$_{93}$N$_8$O$_8$$^{7+}$ 1017.7116 found: 1017.7171; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9196.

6.4.18 Synthesis of Tetrakis-((*N*-dodecyl-imidazoliumyl-acetayloxy)methyl)meth-ane bis(trifluoromethylsulphonyl)amide (10f)

This compound was prepared analogously to **10a** using tetrakis-((*N*-dodecyl-imida-zoliumyl-acetayloxy)methyl)methane chloride **8f** (1.39 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 93% yield (2.20 g). Molecular Formula:

$C_{81}H_{128}F_{24}N_{12}O_{24}S_8$; mol. wt.: 2366.40; FTIR (cm^{-1}): 3073 (C-H)$_{Ar}$, 2959, 2928, 2850 (C-H)$_{Aliph}$, 1757 (C=O), 1652 (C=N), 1565, 1460 (C=C)$_{Ar}$, 1359, 1225 (C-F), 1354, 1140 (O=S=O), 1205, 1179 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.08 (bt~s, 4H, C-H$_{Imidazole}$, minor), 9.03 (bt~s, 4H, C-H$_{Imidazole}$, minor), 8.99 (bt~s, 4H, C-H$_{Imidazole}$, major), 7.80 (t, J=1.81, 4H, C-H$_{Imidazole}$, major), 7.74 (t, 4H, C-H$_{Imidazole}$, minor), 7.63 (t, J=1.81, 4H, C-H$_{Imidazole}$, major), 7.60 (t, 4H, J=1.81, C-H$_{Imidazole}$, minor), 5.45 (s, 8H, O-CH$_2$), 4.33 (t, J= 7.12 Hz, 8H, α-CH$_2$), 4.22 (s, 8H, N-CH$_2$), 1.90-1.86 (m, 8H, β-CH$_2$), 1.32 (bs, 72H, bulk-CH$_2$), 0.90 (t, 12H, J =7.07 Hz, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 168.88 (C=O, minor), 167.83 (C=O, major), 138.77 (CH$_{Imidazole}$), 126.26, 123.04, 119.81, 116.58 (q, J=321, CF$_3$), 124.42 (CH$_{Imidazole}$), 121.552 (CH$_{Imidazole}$), 65.03 (CH$_2$-O, minor), 64.87 (CH$_2$-O, major), 51.74 (CH$_2$-N), 50.67 (α-CH$_2$), 42.73 (-C-), 33.15 (ω-2), 31.20, 30.82(2), 30.72, 30.60, 30.26, 30.05 (bulk-CH$_2$), 27.38 (β), 23.78 (ω-1), 14.63 (ω, major), 14.58 (ω, minor). ^{19}F (336, MHz) δ ppm: −80.12; HRMS: m/z, [M^{+4}−3H]−4NTF$_2$$^-$ calcd. for C$_{73}$H$_{125}$N$_8$O$_8$$^{7+}$ 1241.9620 found: 1241.9702; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9157.

6.4.19 Synthesis of Tetrakis-((*N*-benzyl-imidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphfonyl)amide (10g)

This compound was prepared analogously to **10a** using tetrakis-((*N*-benzyl-imidazo-liumyl-acetayloxy)methyl)methane chloride **8g** (1.08 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 96% yield (1.98 g). Molecular Formula: $C_{61}H_{56}F_{24}N_{12}O_{24}S_8$; mol. wt.: 2053.65; FTIR (cm^{-1}): 3079 (C-H)$_{Ar}$, 2977 (C-H)$_{Aliph}$, 1752 (C=O), 1661 (C=N), 1553, 1490 (C=C)$_{Ar}$, 1348, 1222 (C-F), 1370, 1154 (O=S=O), 1209, 1161 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.01 (s, 4H, C-H$_{Imidazole}$, minor), 8.99 (s, 4H, C-H$_{Imidazole}$, minor), 8.98 (s, 4H, C-H$_{Imidazole}$, major), 7.67 (bt~s, 8H, C-H$_{Imidazole}$, minor), 7.64 (bt~s, 8H, C-H$_{Imidazole}$, minor), 7.60 (bt~s, 8H, C-H$_{Imidazole}$, major), 7.56 (bt~s, 8H, C-H$_{Imidazole}$, minor), 7.45-7.29 (m, 20H, C-H$_{Ar}$), 5.46

(s, 8H, Ar-CH$_2$-, minor), 5.44 (s, 8H, Ar-CH$_2$-, minor), 5.42 (s, 8H, Ar-CH$_2$-, major), 5.22 (s, 8H, O-CH$_2$, minor), 5.20 (s, 8H, O-CH$_2$, major), 4.31 (s, 8H, N-CH$_2$, major), 4.28 (s, 8H, N-CH$_2$, minor), 4.25 (s, 8H, N-CH$_2$, minor); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 168.87 (C=O, minor), 167.64 (C=O, major), 138.81 (CH$_{Imidazole}$, minor), 138.76 (CH$_{Imidazole}$, major), 135.10 (-C$_{Ar}$-CH$_2$-, minor), 134.98 (-C$_{Ar}$-CH$_2$-, major), 130.66 (3 × CH$_A$), 129.91 (2 × CH$_{Ar}$), 126.10, 122.91, 119.72, 116.54 (q, J=320, CF$_3$), 125.63 (CH$_{Imidazole}$), 123.72 (CH$_{Imidazole}$) 123.71 (CH$_{Imidazole}$, major), 64.48 (CH$_2$-O, minor), 64.40 (CH$_2$-O, minor), 64.32 (CH$_2$-O, major), 54.51 (CH$_2$-N), 50.98 (Ar-CH$_2$-), 41.71 (-C-). ^{19}F (336, MHz) δ ppm: −80.23; HRMS: m/z, [M^{+4}–3H]−4NTF$_2^-$ calcd. for C$_{53}$H$_{53}$N$_8$O$_8$$^{7+}$: 929.3986, found: 929.4033; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2^-$: 279.9173, found: 279.9158.

6.4.20 Synthesis of Tetrakis-((*N*-butyl-benzimidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphonyl)amide (11b)

This compound was prepared analogously to **10a** using tetrakis-((*N*-butyl-benzimidazoliumyl-acetayloxy)methyl)methane chloride **9b** (1.14 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 94% yield (2.00 g). Molecular Formula: C$_{65}$H$_{72}$F$_{24}$N$_{12}$O$_{24}$S$_8$; mol. wt.: 2117.81; FTIR (cm^{-1}): 3135 (C-H)$_{Ar}$, 2953, 2928, 2857 (C-H)$_{Aliph}$, 1750 (C=O), 1625 (C=N), 1566, 1470(C=C)$_{Ar}$, 1361, 1222 (C-F), 1361, 1162 (O=S=O), 1202 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 10.53 (s, 4H, C-H$_{BImidazole}$, major), 10.46 (s, 4H, C-H$_{BImidazole}$, minor), 9.37 (s, 4H, C-H$_{BImidazole}$, minor), 8.12-8.03 (m, 8H, C-H$_{BImidazole}$), 7.58-7.41 (m, 8H, C-H$_{Ar}$), 5.95 (s, 8H, O-CH$_2$, major), 5.88 (s, 8H, O-CH$_2$, minor), 4.56 (t, J=7.32, 6H, α-CH$_2$, major), 4.51 (t, J=7.32, 8H, α-CH$_2$, minor), 4.23 (s, 8H, N-CH$_2$), 1.92-1.87 (m, 8H, β-CH$_2$), 1.33-1.26 (m, 8H, (ω-1)-CH$_2$), 0.88 (t, J=7.32, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 167.22 (C=O, minor), 167.60 (C=O, major), 143.21 (CH$_{BImidazole}$), 132.30 (C$_{Ar}$), 131.60 (C$_{Ar}$), 126.87 (CH$_{Ar}$), 126.62 (CH$_{Ar}$), 124.24, 121.03, 117.82, 114.61 (q, J=321, CF$_3$), 114.73

(CH$_{Ar}$), 113.85 (CH$_{Ar}$), 64.09 (CH$_2$-O, minor), 63.82 (CH$_2$-O, major), 46.68 (CH$_2$-N), 46.42 (α-CH$_2$), 40.72 (-C-), 31.23 (ω-2), 20.06 (ω-1), 13.45 (ω). ^{19}F (336, MHz) δ ppm: −80.00; HRMS: m/z, [M^{+4}–3H]−4NTF$_2$$^-$ calcd. for C$_{57}$H$_{69}$N$_8$O$_8$$^{7+}$: 993.5238, found: 993.5241; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9177.

6.4.21 Synthesis of Tetrakis-((*N*-hexyl-benzimidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphonyl)amide (11c)

This compound was prepared analogously to **10a** using tetrakis-((*N*-hexyl-benzimidazoliumyl-acetayloxy)methyl)methane chloride **9c** (1.25 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 98% yield (2.18 g). Molecular Formula: C$_{73}$H$_{88}$F$_{24}$N$_{12}$O$_{24}$S$_8$; mol. wt.: 2230.03; FTIR (cm^{-1}): 3130 (C-H)$_{Ar}$, 2942, 2923, 2863 (C-H)$_{Aliph}$, 1758 (C=O), 1622 (C=N), 1559, 1487 (C=C)$_{Ar}$, 1355, 1223 (C-F), 1362, 1172 (O=S=O), 1202 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.79 (s, 4H, C-H$_{BImidazole}$, minor), 9.76 (s, 4H, C-H$_{BImidazole}$, minor), 9.71 (s, 4H, C-H$_{BImidazole}$, major), 8.06-7.97 (m, 8H, C-H$_{BImidazole}$), 7.78-7.61 (m, 8H, C-H$_{Ar}$, major), 7.47-7.38 (m, 8H, C-H$_{Ar}$, minor), 5.65 (s, 8H, O-CH$_2$, major), 5.62 (s, 8H, O-CH$_2$, minor), 4.54 (t, *J*=7.32, 6H, α-CH$_2$, major), 4.41 (t, *J*=7.32, 8H, α-CH$_2$, minor), 4.22 (s, 8H, N-CH$_2$), 1.98-1.92 (m, 8H, β-CH$_2$), 1.20 (bs, 24H, bulk-CH$_2$), 0.90 (t, *J*=7.07, 12H, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.69 (C=O, major), 167.59 (C=O, minor), 144.07 (CH$_{BImidazole}$), 133.33 (C$_{Ar}$), 132.60 (C$_{Ar}$), 128.80 (CH$_{Ar}$), 128.63 (CH$_{Ar}$), 126.20, 122.99, 119.78, 116.57 (q, *J*=319, CF$_3$), 114.81 (2) (CH$_{Ar}$), 68.09 (CH$_2$-O, minor), 67.87 (CH$_2$-O, major), 46.72 (CH$_2$-N), 41.73 (α-CH$_2$), 40.51 (-C-), 33.19 (ω-2), 27.60 (bulk-CH$_2$), 23.88 (β), 20.10 (ω-1), 14.60 (ω). ^{19}F (336, MHz) δ ppm: −79.40; HRMS: m/z, [M^{+4}–3H]−4NTF$_2$$^-$ calcd. for C$_{65}$H$_{85}$N$_8$O$_8$$^{7+}$: 1105.6490, found: 1105.6445; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9162.

6.4.22 Synthesis of Tetrakis-((*N*-octyl-benzimidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphonyl)amide (11d)

This compound was prepared analogously to **10a** using tetrakis-((*N*-octyl-benzimidazoliumyl-acetayloxy) methyl)methane chloride **9d** (1.36 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 98% yield (2.29 g). Molecular Formula: C$_{81}$H$_{104}$F$_{24}$N$_{12}$O$_{24}$S$_8$; mol. wt.: 2342.24; FTIR (cm^{-1}): 3132 (C-H)$_{Ar}$, 2932, 2920, 2856 (C-H)$_{Aliph}$, 1748 (C=O), 1618 (C=N), 1563, 1487 1462 (C=C)$_{Ar}$, 1362, 1225 (C-F), 1354, 1170 (O=S=O), 1197(C-O); ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) δ ppm: 10.01 (s, 4H, C-H$_{BImidazole}$, minor), 9.96 (s, 4H, C-H$_{BImidazole}$, major), 8.17-8.04 (m, 8H, CH$_{Ar}$), 7.72-7.65 (m, 8H, CH$_{Ar}$), 5.64 (s, 8H, O-CH$_2$, minor), 5.53 (s, 8H, O-CH$_2$, major), 4.57 (t, *J*=7.58, 8H, α-CH$_2$, major), 4.50 (t, *J*=7.58, 8H, α-CH$_2$, minor), 3.33 (s, 8H, N-CH$_2$, minor), 3.26 (s, 8H, N-CH$_2$, major), 1.93-1.86 (m, 8H, β-CH$_2$), 1.22 (bs, 40H, bulk-CH$_2$), 0.83 (t, 12H, *J*=6.60, ω-CH$_3$); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) δ ppm: 168.04 (C=O, major), 166.68 (C=O, minor), 143.32 (CH$_{BImidazole}$,), 131.71 (C$_{Ar}$), 130.75 (C$_{Ar}$), 126.98 (CH$_{Ar}$), 126.71 (CH$_{Ar}$), 124.40, 121.21, 118.01, 114.81 (q, *J*=322, CF$_3$), 113.98 (CH$_{Ar}$), 113.76 (CH$_{Ar}$), 62.12 (CH$_2$-O), 47.61 (CH$_2$-N), 46.95 (α-CH$_2$), 38.27 (-C-), 31.21 (ω-2), 28.55 (2), 28.44 (bulk-CH$_2$), 25.74 (β), 22.11 (ω-1), 14.07 ((ω), minor), 13.90 ((ω), major). ^{19}F (336, MHz) δ ppm: −80.20; HRMS: m/z, [M^{+4}−3H]−4NTF$_2$$^-$ calcd. for C$_{73}$H$_{101}$N$_8$O$_8$$^{7+}$: 1217.7742, found: 1217.7675; m/z, [NTF$_2$]$^-$ calcd. for C$_2$F$_6$NO$_4$S$_2$$^-$: 279.9173, found: 279.9212.

6.4.23 Synthesis of Tetrakis-((*N*-decyl-benzimidazoliumyl-acetayloxy)methyl)methane bis(trifluoromethylsulphonyl)amide (11e)

This compound was prepared analogously to **10a** using tetrakis-((*N*-decyl-benzimidazoliumyl-acetayloxy)methyl)methane chloride **9e** (1.48 g, 1.0 mmol) and Lithium bis-(trifluoromethanesulphonyl)imide LiNTf$_2$ (1.29 g, 4.5 mmol) to give a clear viscous hygroscopic liquid at room temperature in 98% yield (2.41 g). Molecular Formula:

C$_{89}$H$_{120}$F$_{24}$N$_{12}$O$_{24}$S$_8$; mol.wt.: 2454.45; FTIR (cm^{-1}): 3130 (C-H)$_{Ar}$, 2950, 2923, 2822 (C-H)$_{Aliph}$, 1749 (C=O), 1625 (C=N), 1566 1485, 1463 (C=C)$_{Ar}$, 1369, 1219 (C-F), 1358, 1165 (O=S=O), 1219,1199 (C-O); ^{1}H-NMR (400 MHz, CD$_3$OD) δ ppm: 9.56 (s, 4H, C-H$_{BImidazole}$, minor), 9.43 (s, 4H, C-H$_{BImidazole}$, major), 9.39 (s, 4H, C-H$_{BImidazole}$, minor), 8.04-7.80 (m, 8H, CH$_{Ar}$), 7.75-7.48 (m, 8H, CH$_{Ar}$), 5.51 (s, 8H, O-CH$_2$, minor), 5.50 (s, 8H, O-CH$_2$, minor), 5.49 (s, 8H, O-CH$_2$, major), 4.58 (t, J=7.25, 8H, α-CH$_2$), 4.37 (s, 8H, N-CH$_2$, minor), 4.32 (s, 8H, N-CH$_2$, major), 2.07-1.94 (m, 8H, β-CH$_2$), 1.29 (bs, 56H, bulk-CH$_2$), 0.88 (t, 12H, J=6.80, ω-CH$_3$); ^{13}C-NMR (100 MHz, CD$_3$OD) δ ppm: 167.66 (C=O), 143.99 (CH$_{BImidazole}$, major), 142.84 (CH$_{BImidazole}$, minor), 133.22 (C$_{Ar}$), 132.56 (C$_{Ar}$), 128.59 (2 × CH$_{Ar}$, major), 128.44 (2 × CH$_{Ar}$, minor), 126.17, 122.94, 119.72, 116.49 (q, J=322, CF$_3$), 114.78 (2 × CH$_{Ar}$), 64.84 (CH$_2$-O, major), 64.12 (CH$_2$-O, minor), 50.93 (CH$_2$-N), 45.95 (α-CH$_2$, major), 45.32 (α-CH$_2$, minor), 43.79 (-C-), 33.17 (ω-2), 30.83, 30.72, 30.65, 30.53, 30.26 (bulk-CH$_2$), 27.58 (β-CH$_2$), 24.36 ((ω-1), minor), 23.85 ((ω-1), major), 14.57 (ω). ^{19}F (336, MHz) δ ppm: −80.03.

6.4.25 Liquid crystal behaviour

The liquid crystalline properties of compounds **8b-f** and **9b-f** were investigated thermotropically and lyotropically by an optical polarising microscopy. A contact penetration technique (Rendall *et al.*, 1983) was applied in lyotropic investigation with two different types of solvent, one of which is polar (water) and the other non-polar (1-undecanol). It was carried out at room temperature (around 25 °C). The images were recorded at 10× magnification.

6.4.26 Air-water interface tension

The critical micelle concentration (CMC) was determined based on surface tension measurement by applying DuNouy ring method. The surface tensions were measured using a KSV Sigma 702 tensiometer at 25 ± 0.5°C in five replications for each

measurement with a standard deviation of less than 0.1 mN m^{-1}. From surface tension plot against logarithmic concentration, the critical micelle concentration was obtained from the intersection of two regression lines, where one of them is concentration dependent. Solutions were prepared using deionised water with surface tension of 71.96 ± 0.09 mN m^{-1}.

6.4.27 Krafft point (T$_K$)

The Krafft temperature, (T_k), was determined by applying slow heating of 1 % (w/v) aqueous solution of ILs surfactant in a water bath. The solution samples were heated on an IKA hot plate stirrer equipped with temperature controller IKA ETS-D4 at 5 ℃. min^{-1} over the range of 10 ℃ to 50 ℃. The temperature of the clear solution formed was observed while using optical monitoring for transparency changes (Piasecki & Piłakowska-Pietras, 2007).

6.7.28 Closed Bottle Test

'Closed-Bottle Test' (OECD 301D)(Gathergood & Scammells, 2002) was used to evaluate the biodegradability of tetrakis-imidazolium and benzimidazolium ILs (*i.e.* **8b-g** and **9b-g**). The test method was based on biochemical oxygen demand (BOD) due to IL microbial degradation (Coleman & Gathergood, 2010). The BOD values were derived from the quantified respirometric dissolved oxygen (DO) in a culture containing either IL or sodium *n*-dodecyl sulphate (SDS) as a reference sample. CyberScan dissolve oxygen meter DO300 (Eutech Instruments; The Netherlands) was used for DO measurements.

Capped Scotch bottles containing 100 ml solution of 100 mg/L concentration IL or reference sample in distilled water were used to prepare test samples that inoculated with 1 mL of microbial effluent collected from a wastewater treatment plant. Three groups of samples were prepared as the following: inoculum and IL samples in Group 1,

Group 2 contained only the inoculum (test blank), while the inoculum and SDS reference sample were in Group 3. The bottles of solutions were incubated in the dark at 25 ±1°C for 28 days under continuous shaking (200 rpm). The DO values were recorded after every 48 hours where each group sample was replicated 3 times. Since the majority of biodegradation changes were only noticed within the first 16 days period of time, the results of days 10 and 16 were considered.

Equation (6.1) was considered to calculate the BOD values based on observed DO (Massardier-Nageotte *et al.*, 2006) as follows:

$$BOD = \frac{DO_o - DO_t}{\varphi} \qquad (6.1)$$

Where DO_o is initial dissolved oxygen and DO_t is the dissolved oxygen at time t. While φ is fractional oxygen volume defined as the ratio of the experimental DO volume to the theoretical DO volume that obtained from the reference sample.

Further, the percentage biodegradability was calculated according to the expression in the following equation (6.2) (Coleman & Gathergood, 2010):

$$Biodegradation = \frac{BOD}{ThOD \left(\frac{mg\ O_2}{mg\ sample\ weight}\right)} \times 100 \qquad (6.2)$$

where $ThOD$ represents the theoretical oxygen demand which is defined as the amount of oxygen consumed by the microorganisms in the sample corrected for the uptake of O_2 by the blank inoculums (Coleman & Gathergood, 2010).

CHAPTER 7: CONCLUSION AND RECOMMENDATIONS

7.1 CONCLUSION

Novel sets of bis-, tris- and tetrakis-imidazolium and benzimidazolium ILs incorporated into halogens, were successfully synthesized from readily available starting materials in high yield and purity. Metathesis of halogen anion to NTf$_2$ tuned all ILs to clear liquids at room temperature. The structures of these multi-cationic ILs were confirmed by classical FTIR, NMR, and HRMS techniques.

Thermal stability as well as *in vitro* antibacterial activities against ten strains of bacteria of all synthesized halogens geminal di-imidazolium and di-benzimidazolium ILs were evaluated. The miscibility of the prepared ILs in both water and common organic solvents are indicated as well. The present of the high rigid spacer incorporated into benzenesulphonamide moiety beside various active side substituents promoted their antibacterial activities and miscibility in polar and non-polar solvents. Generally, the geminal ILs bearing imidazolium di-cationic exhibited higher results of antibacterial and onset decomposition temperature as compared to those with benzimidazolium.

The factors that improved the biodegradation of surfactants have successfully been used to develop the biodegradation and self-assemble behaviour of the synthesized tri- and tetra-cationic ILs. Comparing to traditional mono-cationic ILs, both imidazolium and benzimidazolium ILs showed enhancement in the biodegradation due to the presence of tri- and tetra-ester groups incorporated into alkyl or phenyl side chains. The tris- and tetrakis-imidazolium ILs effectively reduced the water surface tension to a range of 29– 34 mN m^{-1}; in addition, they displayed significant increase in phase behaviour properties and biodegradation comparing to benzimidazolium ILs. Further, the developed properties of synthesized tri- and tetra-cationic ILs are highly enhanced by increasing the ILs hydrophobicity. Precisely, ILs incorporating the long linear alkyl

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(*i.e.* octyl, decyl, dodecyl) in the side chains are presented on the border of the 60% pass level of readily biodegradation results with capability to self-assemble spontaneously or in the presence of a solvent.

7.2 RECOMMENDATIONS FOR FUTURE RESEARCH

The current work leads to the following suggestions for future work:-

1) The successful synthesis of current tri- and tetra-cationic ILs encouraged going straightforward for synthesis hexa-cationic IL based on current methodology.

2) Investigated surface properties including critical micelle concentration (CMC), surface tension γ_{cmc}, Krafft temperature and Cloud point as well as more physical properties of the synthesized dicationic ILs (*e.g.*, viscosity and fluorescence) towards gemini-type ILs surfactant with broad practical applications in industry and medicine.

3) Study counter-ion effect of tri and tetra-cationic imidazolium and benzimidazolium ILs on biodegradation towards *readily biodegradable* (60% degradation within the test period).

4) Explore more effective surfactant from current tri- and tetra-cationic ILs incorporated with NTf_2 as counter-ions, since the fluorine compounds successfully reduce water surface tension.

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