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Feature Article

Imidazole- and imidazolium-containing polymers for biology and material science applications

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ABSTRACT

The imidazole ring is ubiquitous in nature and imidazole functionality plays a critical role in many structures within the human body, notably as histamine and histadine. Imidazoles offer many biophysical interactions including their ability to hydrogen bond with drugs and proteins. In contrast, imidazolium salts have lost their strong hydrogen-bonding ability through alkylation of both nitrogens, but they are able to aggregate electrostatically. Imidazolium salts are used to extract metal ions from aqueous solutions, dissolve carbohydrates, create polyelectrolyte brushes on surfaces, coat metal nanoparticles, provide antimicrobial action, and create oriented liquid crystals. Bioactive applications include imidazolium hydrogels, antiarrhythmics, and anti-metastic agents. This review will describe the synthesis and design of imidazole derivatives and imidazolium-containing polymers as bioactive materials. Imidazole-based polymers readily associate with biological molecules through hydrogen-bonding, and imidazolium analogs offer electrostatic interactions, aggregation, and self-assembly. Design of novel imidazole- and imidazolium-based macromolecules remains as an exciting and emerging field.

1. Introduction

1.1. Introduction to imidazole- and imidazolium salts: application

From clicking drugs onto the backbones of delivery vectors [1] to synthesizing N-heterocyclic carbene ligands for antitumor compounds [2], nitrogen heterocycles have a long history in biomedical research and remain a front-runner for bioactive applications. Imidazoles and their salts in particular comprise a boundless and emerging field. The polar imidazole ring, which contains two nitrogens separated with a methylene, hydrogen bonds through the amino hydrogen as the donor and the imino nitrogen as the acceptor (Fig. 1) [3,4].

Many uses of the imidazole ring as a bioagent revolve around its ability to bond to metals as a ligand [5–9] and its ability to hydrogen bond with drugs and proteins. This aptitude has resulted in the use of polyimidazoles as oxygen transport membranes [8]. Furthermore, chemical modification of the imidazole functionality has led to desired covalent or physical crosslinking and the production of functional or multifunctional polymers [10]. The imidazole ring's biocompatibility provides a scaffold for biomimetic applications [9], including the use of imidazoles as DNA sequence targets for alkylating DNA and suppressing gene expression [11]. Not only are imidazoles biocompatible, but they also are antimicrobial. The 1-alkyl imidazoles offer antibacterial activity [12], and imidazoles inhibit enzymes and kill fungal pathogens [12]. Imidazoles also play a role in inhibition of post-translational farnesylation, which is a key step for Ras proteins that influence cancer proliferation [12]. The amino acid histamine, a naturally occurring imidazole in the body, is involved with everyday functions: sleeping, eating, drinking, and cognitive processes [12]. Imidazole-based antagonists for histamine may provide treatments for Alzheimer's disease and depression [4,12]. Vitamin B_{12}, DNA purines, and biotin all involve imidazole residues [4,12,13]. Imidazoles are also anti-inflamatory agents and regulate blood pressure [13]. They offer high thermal stability and are often used in high temperature polymeric products [4,14]. The imidazole ring offers high chemical stability, stability to harsh acids and bases, and resistance to hydrogenation. However, it undergoes several typical aromatic substitution reactions to provide functional derivatives [4,14].

Despite the loss of directed, self-complementary hydrogen bonding through alkylation of the imidazole ring, electrostatic aggregation of imidazolium salts is a tunable, self-assembly process, which is instrumental to several applications. Imidazolium salts are used to extract metal ions from aqueous solutions and coat metal nanoparticles [15], dissolve carbohydrates [16], and create polyelectrolyte brushes on surfaces [17]. For example, atom transfer radical polymerization (ATRP) was used to graft poly(1-ethyl

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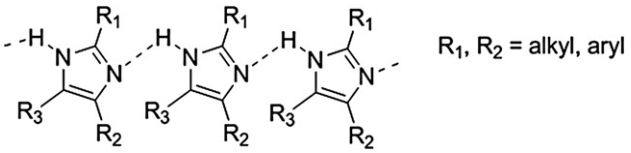

Fig. 1. General imidazole structure with self-complementary hydrogen bonding [3]. Reprinted with permission from Ref. [12]. Copyright 1984 American Chemical Society.

3-(2-methacryloyloxy ethyl) imidazolium chloride) brushes onto gold surfaces [17]. One of the imidazolium salt's most promising attributes is its antimicrobial action [12,18] and molecular self-assembly into liquid crystals [19,20]. 1-Alkyl-3-methylimidazolium chlorides and bromides, 1-alkyl-2-methyl-3-hydroxyethylimidazolium chlorides, and *N*-alkyl-*N*-hydroxyethylpyrrolidinonium, for example, all exhibit strong biocidal activity [18]. Hydrogels form from polymerized methylimidazolium-based ionic liquids with acryloyl groups; the polymer self-assembles into organized lamellae with unique swelling properties, leading to bioactive applications [19]. Other bioactive applications for imidazolium salts include antiarrhythmics [21], anti-metastic agents [22,23], and imidazolium-based steroids [24]. Separation applications include efficient absorption of CO_2 [25]. Imidazolium salts enhance vesicle formation as imidazolium surfactants [26], and they also find application in polymeric actuators [27].

The imidazole ring and its salts afford a wealth of biophysical-related applications, and attachment of imidazole derivatives to polymers represents a new and relatively unexplored field. The supramolecular association of novel imidizolium-containing biopolymers for antimicrobial and antimycotic drug applications receives significant attention. Weak ionic interactions may facilitate bioactivity and selectivity.

1.2. Imidazole ring: biology and physical attributes

De Luca provided a focused earlier view of imidazoles with concentration on their current use as bioactive compounds [12], and she outlined the roles of imidazoles in antibiotics to anti-inflammatory agents. Several imidizole structures exist in nature. Histamine is one of the most important and has potent physiological effects [12,28] Fig. 2.

Imidazolium ionic liquids offer templates for synthesis of functionalized carbohydrates [16,29]. Carbohydrates bind to proteins and control synthon transfer between cells [16,29]. Imidazolium-based steroids were reported [24], and imidazolium salts serve as antiarrhythmics [21] and anti-metastic agents [2,22,23]. Lee et al. investigated the antimicrobial and antifungal properties of several imidazolium salts that inhibited growth of gram-negative bacteria, gram-positive bacteria, and fungi [18].

Cytotoxicity and *in vitro* behavior of imidazolium-based polymers are relatively unexplored. Toxicity of imidazolium ionic liquids and other small molecules show the general trend that cytotoxicity is highly dependent on the counter anion and the length of any alkyl chains on the nitrogens of the imidazole ring. Longer alkyl chains increase the cytotoxicity [30]. Imidazolium salts

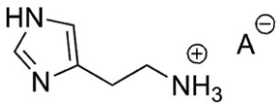

Fig. 2. Histamine at physiological pH, A is the counter anion and has numerous possibilities, including chloride and heparin. Reprinted with permission from Ref. [28]. Copyright 1975 American Chemical Society.

were found to have anti-fibrotic properties in mouse hepatic stellate cells. This finding indicates that these imidazolium salts prevent liver fibrosis [31]. These salts also possess anti-metastic properties [32]. However, imidazolium-based *polymer in vitro* studies offer a huge area for future research.

Dupont and Suarez recently reviewed the physical properties of imidazolium salts, specifically imidazolium ionic liquids [33]. The desirable chemical and thermal stability of the imidazolium ring was noted, as well as interesting solubility and conductivity. Large cations hinder allocation into a lattice, and, therefore, ionic compounds with low lattice energies exist as ionic liquids at temperatures below 100 °C [33–37], and room temperature ionic liquids are particularly attractive. The low melting point of imidazolium salts derives from large cations requiring lower energy to break electrostatic interactions. Adding long alkyl chains to these salts decreases both packing ability and lattice energy to depress the melting point. Asymmetry also negatively influences ordering and promotes low melting salts. Long-range Coulomb interactions in ionic liquids promote longer spatial correlations than van der Waals forces [33–38]. The 1,3-dialkylimidazolium cations form cationic and anionic channels where three anions flank each cation and vice versa [33]. The fluid structure is considered self-assembled and supramolecular. Imidazolium ionic liquids also have high thermal stability [33,39]. Dupont and Suarez outlined how decomposition of imidazolium salts follows several pathways, including 2-position deprotonation to form carbenes (pka 21-23) [33,40–45] and Hoffman elimination [33,46,47].

Imidazolium salts enable many emerging applications including nanocomposites [33,48–58], reaction solvents [33], and CO_2 absorbents [25]. These salts form self-assembled monolayers [15], create one-dimensional ion conduction for columnar, uniaxially oriented liquid crystals, and enhance vesicle formation [26]. Some imidazolium salts are liquid crystals and possess ion conductivity [33,59,60]. Most imidazolium salts show relatively higher solubility of CO_2 compared to O_2 and other gases, which derives from weak Lewis acid–base interactions with anions [25,61]. Electron-rich metals or even metals in nanoparticles cause carbene formation of 4- and 5-imidazole ring positions due to their lower acidity than the 2 position [33,62–64]. Imidazolium coated and functionalized nanoparticles exist [15], and stabilization of nanoparticles in imidazolium ionic liquids occurs through surfactant-like interactions [65,66].

2. Imidazole- and imidazolium-based polymers

Although the scope of published reactions involving imidazole ring formation is too large to review in this document, Grimmett outlined key approaches to various substituted imidazoles [14]. The Weidenhagen synthesis, for example, involves α-hydroxyketones that are oxidized to dicarbonyls with cupric acetates [4]. A hydroxyketone is converted to a ketoaldehyde or diketone, and a cuprous ion is created. The aldehyde, dicarbonyl-contain compound, and ammonia react to form an imidazole cuprous complex. Hydrogen sulfide is commonly used to form free imidazole from its metal salt form [4].

Alkylation of imidazoles and imidazolium synthesis is simple compared to their heterocylic ring formation. Alkylation of the secondary amine simply proceeds through deprotonation of the amino hydrogen with a base followed with attack of halogenated alkyls. The second nitrogen is subsequently alkylated in a second reaction with haloalkyls [16]. Fig. 3 exemplifies this strategy for the synthesis of a hydroxyl-containing imidazolium salt.

Many imidazole- and imidazolium-based polymers exist. The vast majority of literature focuses on olefin-containing imidazole monomers. Ferruti et al. synthesized novel alkyl methacrylate-

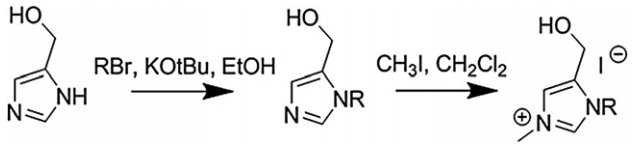

Fig. 3. Koschella et al. present a classic example of the synthesis of imidazolium salts from imidazoles. Reprinted with permission from Ref. [16]. Copyright 2007 American Chemical Society.

based imidazoles as precursors for various functional polymers using poly(hydroxyethyl acrylate) (HEMA) and N,N′-carbonyldiimidazole (CDI) in chloroform at room temperature without a catalyst (Fig. 4) [10].

Liu et al. synthesized novel polyelectrolyte gels for solid-state electrochemical devices as the dye-sensitized solar cell [67]. Their polyelectrolyte gel was based on 1-ethyl-3-(2-methacryloyloxyethyl)imidazolium iodide (PEMEImI). PEMEImI upon addition of I_2 and polyacrylonitrile plasticizers formed a gel with ionic conductivity of 1×10^{-3} S cm^{-1} at room temperature [67]. Having both free anions and cations causes polarization through migration of these charges to opposite electrodes. Immobilizing one of the ions in a polymer reduces resistivity and polarization [67]. Nishide et al. used poly(1-vinyl imidazole)s to coordinate to cobalt oxygen carriers to form reversible oxygen-binding polymer membranes for facilitated oxygen transport (Fig. 5) [8,68].

Firestone et al. studied cation structure as related to the lyotropic mesophase behavior of self-assembled imidazolium ionic liquids and their polymers [20]. Both the effects of alkyl chain length and introducing an acryoyl group for polymerization onto the end of the alkyl were investigated with small angle X-ray scattering (SAXS). Small angle x-ray scattering provides a measure of the distances between phases and ionic aggregates in polymers through x-ray scattering in these regions. This technique is used commonly to study measure the interparticle distance between ionic aggregates in ionomers and polyelectrolytes [20,69–72]. Some ionic liquids self-assemble into strong physical gels upon water addition. Acryloyl groups add photopolymerizable sites to increase the mechanical integrity of these gels. Using an eight-carbon alkyl produced weakly-ordered, lyotropic mesophase, and lamellar structure biomembranes with water channels. The structure was maintained after polymerization. A longer, decyl chain increased order and formed tetragonal perforated structures. Once polymerized, cubic structures were obtained [20]. Firestone et al. also investigated hydrogels, including self-assembly of ionic liquids and subsequent polymerization for biomimetic applications [19]. Polymerization of acryloyl-based imidizolium salts formed hydrogels with a lamellar structure. The gels swelled nearly 200 times their volume, forming disordered lamellae. A physically crosslinked gel that swells to a pre-determined dimension is considered a responsive polymer [19,73]. These types of responsive polymers and hydrogels enabled drug release applications, sensors, and artificial muscles [19].

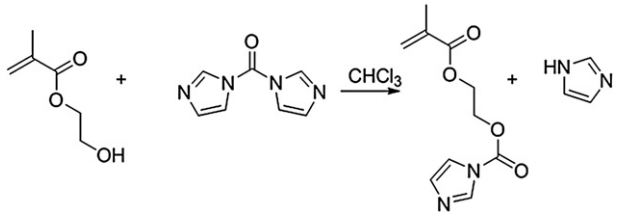

Fig. 4. Synthesis of imidazole vinyl monomer. Copyright 1998 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from Ref. [10].

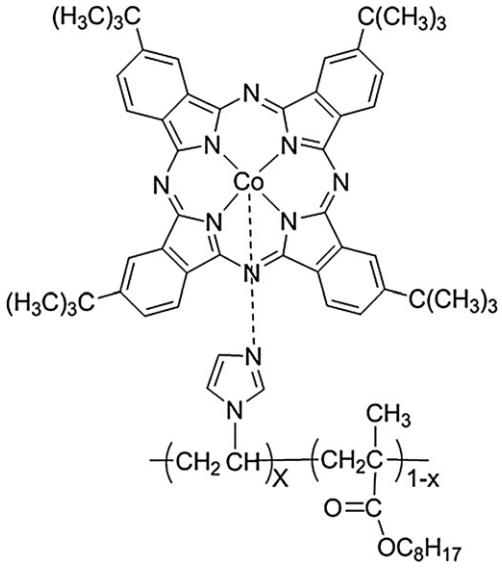

Fig. 5. Poly(1-vinyl imidazole) coordinated to cobalt oxygen carriers. Reprinted from Ref. [8]. Copyright 2006, with permission from Elsevier.

Many other bio-related, imidazole-containing polymers exist. For example, Sugiyama and Bando synthesized N-methylimidazole-containing polyamides for sequence-specific DNA alkylation [11]. They coupled imidazole or pyrrole groups with carboxylic acids to synthesize these polyamides through classical solid-phase peptide synthesis (Fig. 6) [74].

Blocking specific DNA sequences suppresses expression of corresponding genes. Deemed “knowledge-based therapy,” regulating gene expression could in turn silence cancer cell proliferation. These polyamides selectively bound sequences in the minor groove of DNA double helix, allowing alkylating agents to target one sequence (Fig. 7) [11].

The imidazolium salt was selective for G–C base pairs, and gene-silencing did result. These polymers represent a step closer to tailor-made anticancer agents and offer advantages including their automated solid-phase synthesis and flexibility [11]. Besides novel vinyl imidazoles and imidazolium-based polymers, novel imidazolium ionenes [75–78], main-chain metal-coordinated polymers [6], and pseudorotaxanes exist [79].

Ohno et al. synthesized imidazolium salts in the backbone of the polymer, or ionenes, via hydroboration reactions (Fig. 8) [75]. Conductive polyelectrolytes were formed from 1,3-diallylimidazolium bromide. An anion exchange provided lithium bis(trifluoromethylsulfonyl)imide based organoboron polymers. An ionic conductivity of 3.74×10^{-5}–1.93×10^{-5} S cm^{-1} at 50 °C resulted [80]. Anion trapping of organoboron was successful.

In two studies, Ohno and coworkers studied a multitude of different imidazolium-containing polymers and composites where various counterions and structures affected conductivity. They synthesized polyelectrolytes through both the functionalization of imidazolium salts with acrylic groups through DCC coupling reactions with hydroxyl-containing imidazolium salts [80] and reactions between lithium 9-borabicyclo[3,3,1]nonane hydride and 1,3-dihydroxyethyl imidazolium bromide [81]. Anion exchange to bis(trifluoromethylsulfonyl)imide for the later polymers led to high ionic conductivity of 3.4×10^{-6} S cm^{-1} at 50 °C. The glass transition temperature of −6 °C provided promising mechanical properties and high conductivity. Ohno and coworkers also studied nitrile rubber composites imidazolium zwitterions [82]. Addition of imidazolium at 9.2 wt% provided an 8-fold increase in ionic

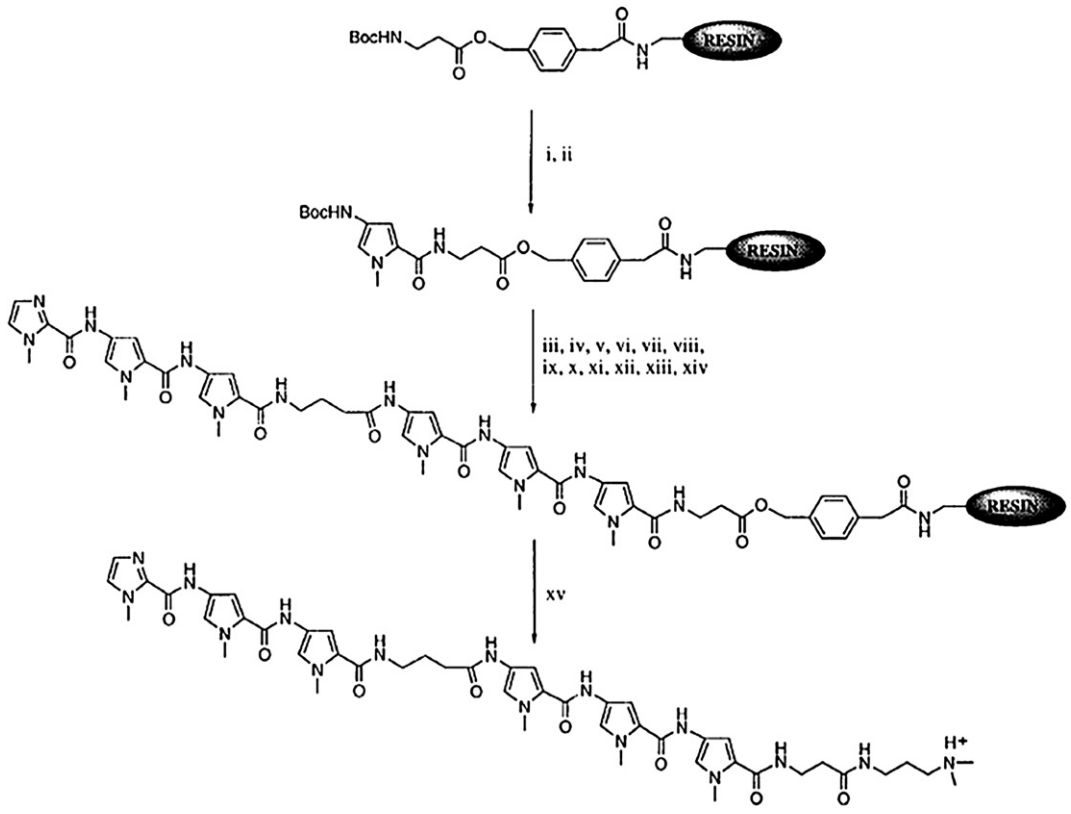

Fig. 6. An example of solid-phase synthesis of a polyamide on a solid support. Reprinted with permission from Ref. [74]. Copyright 1996 American Chemical Society.

conductivity through decreasing the interaction of nitrile rubber with lithium cations. Microphase separation also was observed [82].

Long recently described a facile ionene synthesis from an easily accessible bis-imidazole as illustrated in Fig. 9 [76–78]. This synthesis is facilitated through S_N2 reactions coupling dibromides and diimidazoles and is another rare example in the literature of step-growth methods to imidazolium-containing polymers.

Catalano et al. synthesized silver, gold, and palladium-based imidazole-containing complexes that formed luminescent polymers with in-chain metal coordination [6]. Ghosh et al. used silver imidazole-containing complexes as initiators for ring-opening polymerization of L-lactides in bulk [7]. Ring-opening polymerization of lactide monomers and homogeneous catalysis was achieved.

Bielawski et al. also used step-growth polymerization of bis(N-heterocyclic carbene)s to synthesize poly(enetetramine)s as conjugated polyelectrolytes for biological sensing and electronic applications (Fig. 10) [83,84]. This approach is a novel method to step-growth based imidazolium-containg polymers, but oxidatively unstable polymers were obtained. Polymerization of these monomers provided tailored spectroscopic and electronic properties.

Beer et al. used anion-templated assembly of novel [2] pseudorotaxanes with imidazoliums threading through a chloride

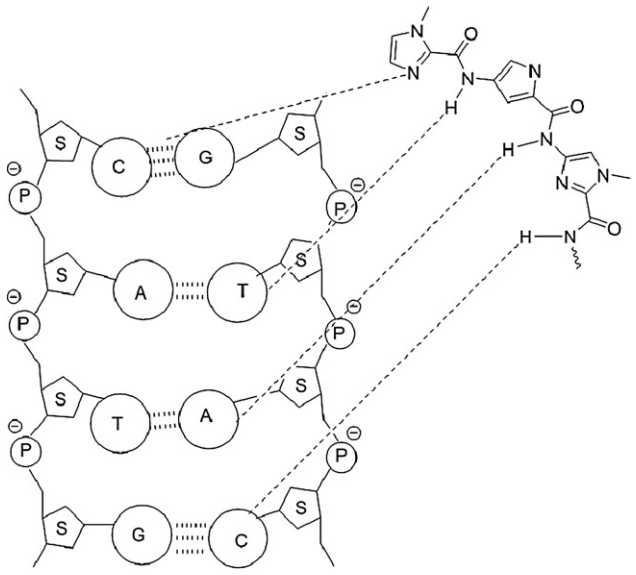

Fig. 7. H-bonding of N-methylimidazole-containing polyamides with DNA for sequence-specific DNA alkylation; G = guanine, C = cytosines, A denine, T = thymine, P phosphate, S = deoxyribose sugar. Reprinted with permission from Ref. [11]. Copyright 2006 American Chemical Society.

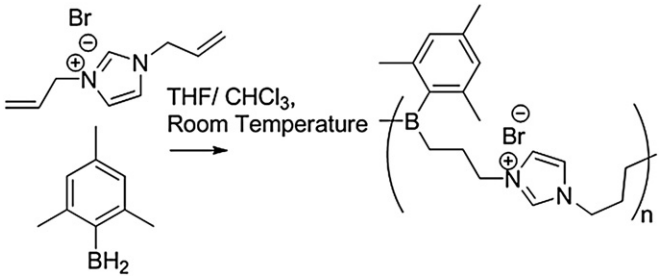

Fig. 8. Imidazolium ionones formed from hydroboration reactions. Reprinted with permission from Ref. [75]. Copyright 2006 American Chemical Society.

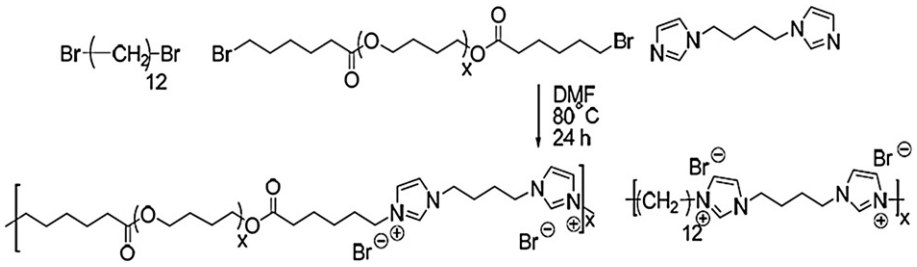

Fig. 9. Synthesis of segmented imidazolium-based ionenes with PTMO soft segments [76–78]. Reprinted from Ref. [76], Copyright 2009, with permission from Elsevier.

anion-based macrocycle to form interlocked structures for use in sensor design (Fig. 11) [79]. Selective anion recognition through electrostatic interactions has spurred interest in recent years [79]. Supramolecular assemblies widely used to create these interlocked structures are hydrogen bonding, π–π stacking, and metal coordination [79–85]. The anion associates with two or more groups [79–85]. In 2006, Kim reviewed the synthesis of imidazolium anion recognition sites and self-assembly [86].

3. Perspective for future studies

Imidazoles are naturally occurring in the human body, and histamine is one of the most important with formidable physiological effects [12]. Physical applications range from gas separation [25] to designed surfactants [26]. imidazole- and imidazolium-based polymers offer new avenues for biocompatibility and antimicrobial activity [18]. Most imidazolium salts have liquid crystalline properties and possess ion conductivity [33]. Imidazole-containing polymers enable hydrogels [19], antiarrhythmics [21], and anti-metastic agents [22,23]. These highly-stable, imidazole-based polymers suggest a plethora of emerging biophysical applications.

Imidazole-based polymers open a new avenue to functional polymers and macromolecular design. The precursor polymer 2-[(1-imidazolyl)formyloxy]ethyl methacrylate (HEMAIm) provides new routes to multiple types of functional polymers, for example (Fig. 12) [10].

Polyamides containing imidazoles that bind to the minor groove of DNA compete with transcription factors and block gene expression. A study utilizing a nude mouse xenograft model showed that these types of polymers did inhibit the growth of estrogen receptors associated with human breast cancer cell Br 10 proliferation [11]. Sequence-specific DNA alkylation to prevent gene expression was achieved, indicating their potential use as antitumor drugs [11].

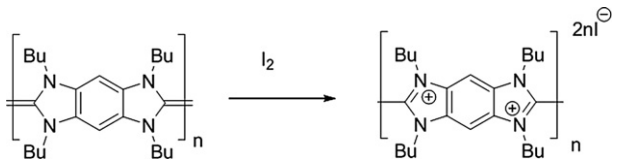

Fig. 10. Synthesis of poly(enetetramine)s. [83] – reproduced by permission of the Royal Chemical Society.

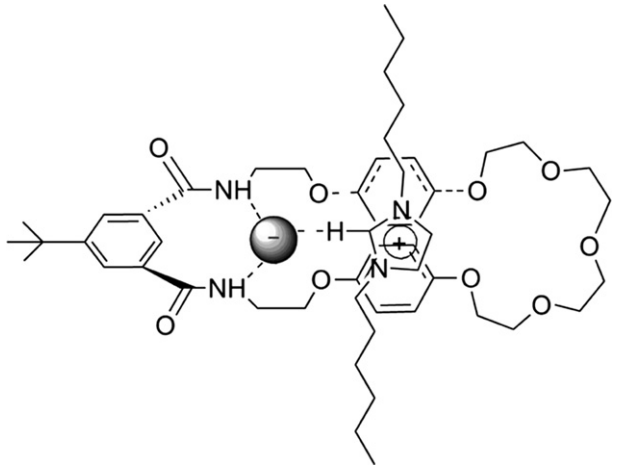

Fig. 11. Imidazoliums threading through a chloride anion-based novel [2] pseudorotaxanes [79] – Adapted by permission of the Royal Chemical Society.

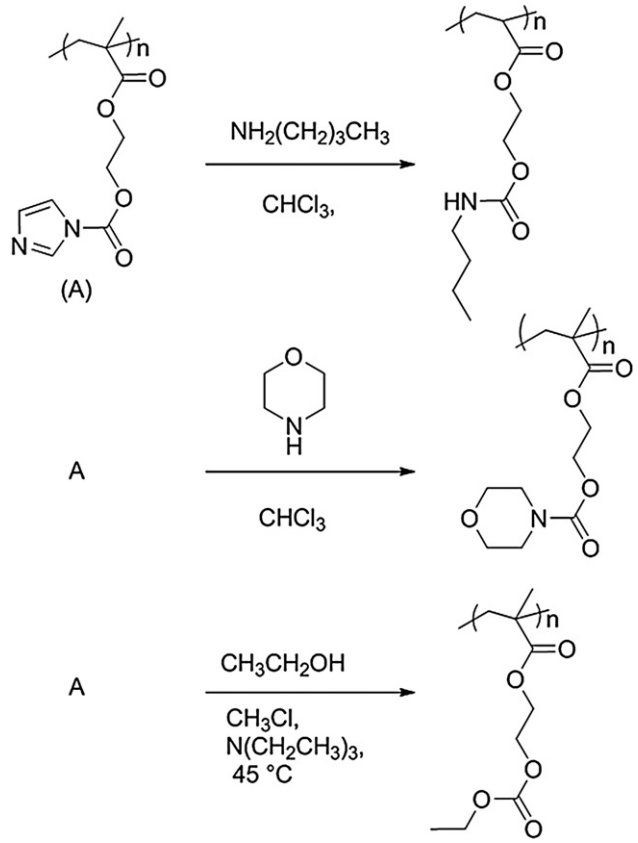

Fig. 12. The versatile nature of the imidazolium backbone in the synthesis of functional polymers. Copyright 1998 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

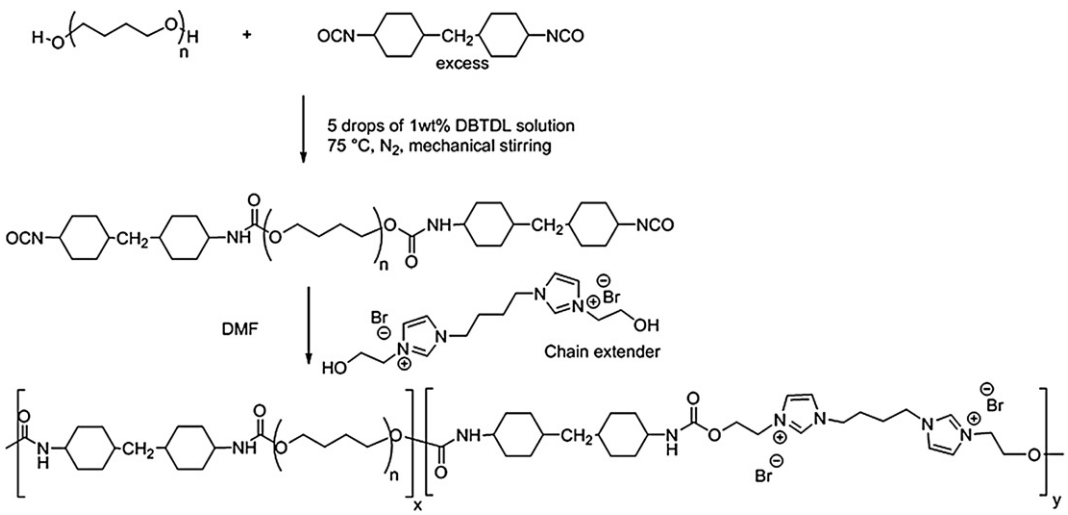

Fig. 13. Polyurethane synthesis with imidazolium diols as a chain extender.

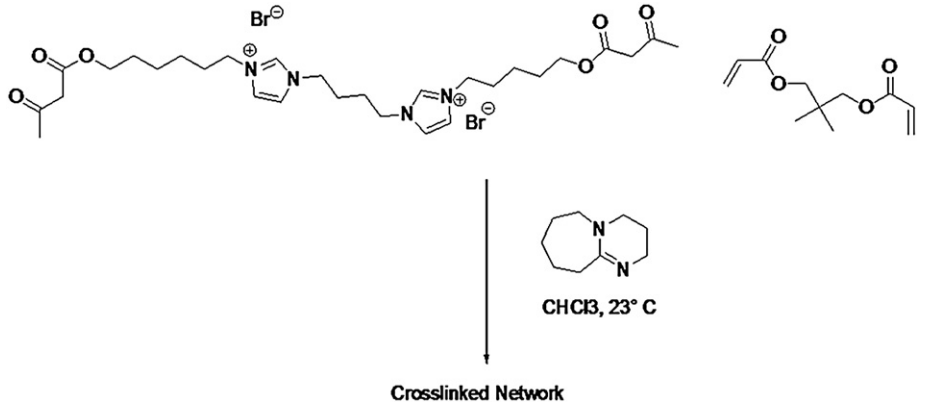

Fig. 14. BisAcAc-imidazolium salts for Michael addition networks.

The versatility of polymeric imidazoles and imidazolium salts extends beyond biology. Metal binding of the imidazole ring allows for oxygen transport. New steps in reversible oxygen-binding imidazole-based polymers complexed to cobalt allowed for the separation of oxygen from air. These polymer membranes achieve a high, oxygen transport of 28 [68]. Furthermore, polyimidazolium electrolyte gels also show promising ionic conductivity above 1×10^{-3} S cm^{-1} [67]. Future development into dye-sensitized solar cells is a growing possibility. Templated assembly of imidazolium-based salts was even possible for rotaxanes with high selectivity, creating some of the first imidazolium-based interlocked catenanes [79].

Step-growth chemistry and covalently crosslinked networks with the imidazolium functionality are especially sparse in the literature. Current efforts in our research group include using imidazolium diols (Fig. 13) and bisAcAc-containing imidazolium salts (Fig. 14) as monomers for both polyurethanes and Michael Addition networks, respectively. These polyurethanes exhibited an ionic cluster transition in DMA, and increasing ionic hard segment content increasingly disrupted the flow region to produce highly physically crosslinked polymers.

We have recently demonstrated the synthesis of imidazolium-containing ionene segmented block copolymers from 1,1′-(1,4-butanediyl)bis(imidazole) and 1,12-dibromododecane and 2000 g/mol PTMO dibromide (Fig. 9) [76–78]. The non-segmented imidazolium ionenes originated from Yanagida et al. [87] and Chen et al. [88] who used alkyl bis(imidazoles) and alkyl diiodides. The target for these original ethylene oxide-based ionenes was dye-sensitized solar cells. Our work involves examining the structure-property

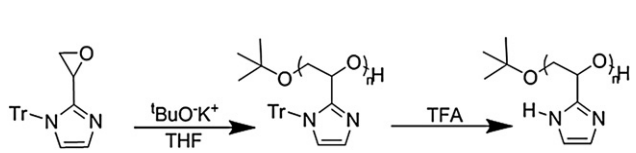

Fig. 15. Anionic ring-opening polymerization of novel *N*-tritylimidazole-2-ethylene oxide. Reprinted with permission from Ref. [89]. Copyright 2009 American Chemical Society.

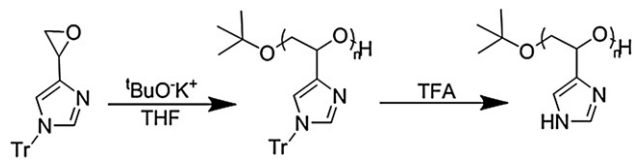

Fig. 16. Anionic ring-opening polymerization of novel *N*-tritylimidazole-4-ethylene oxide. Reprinted with permission from Ref. [89]. Copyright 2009 American Chemical Society.

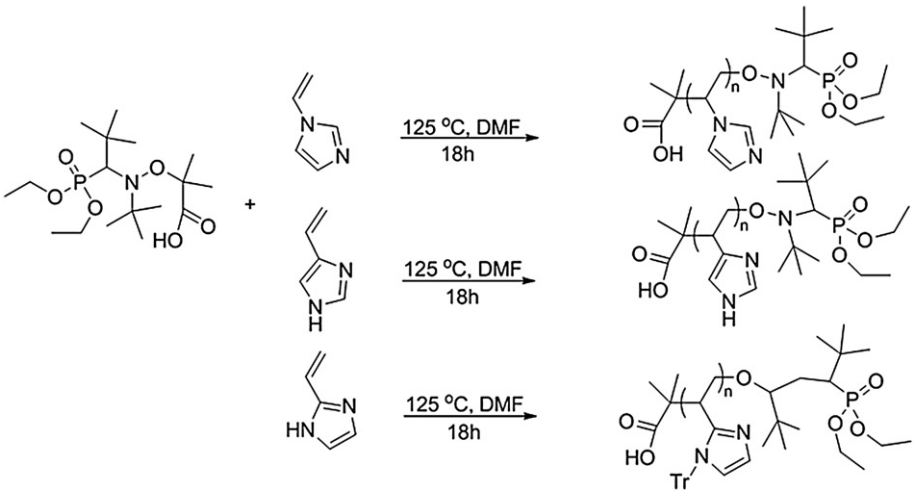

Fig. 17. Synthesis of linear, 1,4, and 2-vinylimidazole-based polymers via living nitroxide-mediated polymerization.

relationships of segmented-based imidazolium ionenes when changing charge density. These PTMO-based imidazolium ionenes possessed crystallinity, melting points near room temperature, and a glass transition temperature of −80 °C. Dynamic mechanical analysis (DMA) and small angle x-ray scattering (SAXS) also indicated microphase separation. The imidazolium ionene control that was not segmented with PTMO sequences had a glass transition of 27 °C [76–78].

In addition to imidazolium-based polyurethanes and ionenes, we also pioneered the synthesis of imidazole-containg epoxide-based monomers and their subsequent ring-opening polymerization for electroactive devices. We have demonstrated the synthesis of *N*-tritylimidazole-2-ethylene oxide and *N*-tritylimidazole-4-ethylene oxide. Polymerization of these monomers was successfully initiated with potassium t-butoxide, and the trityl protecting group was quantitatively removed after polymerization with trifluoroacidic acid (TFA) (Figs. 15 and 16) [89].

Upon deprotection, the imidazole-2-ethylene oxide polymer had a glass transition of 65 °C, slightly higher than the imidazole-4-ethylene oxide containing polymer with a glass transition of 50 °C. We are currently investigating the alkylation of the imidazole backbone with various bromoalkyls to determine structure-property relationships with various levels of alkylation to imidazolium salts. We are also investigating the effect of different vinyl group positions on the thermomechanical properties, fiber formation, biological binding, and conductivity. Additionally, we are exploring the synthesis of linear, living 1-vinylimidazolium, 2-vinylimidazolium, and 4-vinylimidazolium polymers and block copolymers using Blockbuilder™ for nitroxide-mediated polymerization (Fig. 17).

In summary, the design of imidazole derivatives and imidazolium-containing polymers enables many new applications. Imidazole-based polymers readily associate with biological molecules, drugs, metals, and proteins through hydrogen-bonding, and imidazolium derivatives offer electrostatic interactions, aggregation, and structured self-assembly. The authors hope to encourage the design of novel imidazole- and imidazolium-based polymers as a fascinating and promising field.

Many applications exist in biology and material science for these polymers. Studies have investigated the cytotoxicity, antifibrotic, and anti-metastic properties of several small molecule imidazolium salts or ionic liquids *in vitro* [30–32], but *in vitro* study of polymeric imidazolium salts is a new area requiring much research. Investigation of imidazolium-based polymers as transfection agents also is an unexplored area. In material science, imidazolium-based polymers expand the scope of ionic polymers for transducers, actuators, and all other types of responsive applications. Although conductivity measurements indicate that imidazolium-based polymers do improve performance, continued device studies are needed. Overall, a wealth of potential applications and further research exists for imidazolium-based polymers.

References

[1] Kolb HC, Sharpless KB. Drug Discov Today 2003;8(24):1128–37.
[2] Keppler BK, Wehe D, Endres H, Rupp W. Inorg Chem 1987;26:844–6.
[3] Brédas JL, Poskin MP, Delhalle J, André JM, Chojnacki HJ. Phys Chem 1984;88:5882–7.
[4] Hofmann K. The chemistry of heterocyclic compounds, imidazole and derivatives part 1. New York: Interscience Publishers, Inc.; 1953.
[5] Organ MG, Avola S, Dubovyk I, Hadei N, Kantchev EAB, O'Brien CJ, et al. Chem Eur J 2006;12:4749–55.
[6] Catalano VJ, Etogo AO. Inorg Chem 2007;46:5608–15.
[7] Samantaray MK, Katiyar V, Pang K, Nanavati H, Ghosh P. J Organomet Chem 2007;692:1672–82.
[8] Preethi N, Shinohara H, Nishide H. Reactive Funct Polym 2006;66:851–5.
[9] Le Poul N, Campion M, Douziech B, Rondelez Y, Le Clainche L, Reinaud O, et al. Am Chem Soc 2007;129:8801–10.
[10] Ranucci E, Spagnoli G, Ferruti P. Macromol Rapid Comm 1998;20:1–6.
[11] Bando T, Sugiyama H. Acc Chem Res 2006;39:935–44.
[12] De Luca L. Curr Med Chem 2006;13:1–23.
[13] Hamilton CA. Pharmacol Ther 1992;54(3):231–48.
[14] Grimmett MR. Imidazole and benzimidazole synthesis. Academic Press, Inc.; 1997.
[15] Lee S-G. The Royal Society of Chemistry. Chem Comm; 2006:1049–63.
[16] El Seoud OA, Koschella A, Fidale LC, Dorn S, Heinze T. Biomacromolecules 2007;8(9):2629–47.
[17] Yu B, Zhou F, Hu H, Wang C, Liu W. Electrochimica Acta 2007;53:487–94.
[18] Demberelnyamba D, Kim K-S, Choi S, Park S-Y, Lee H, Kim C-J, et al. Bioorg Med Chem 2004;12:853–7.
[19] Batra D, Hay DNT, Firestone MA. Chem Mater 2007;19:4423–31.
[20] Batra D, Seifert S, Firestone MA. Macromol Chem Phys 2007;208:1416–27.
[21] Lis R, Davey DD, Morgan TK, Lumma WC, Wohl RA, Jain VK, et al. J Med Chem 1987;30:2303–9.
[22] Sanna B, Debidda M, Pintus G, Tadolini B, Posadino AM, Bennardini F, et al. Arch Biochem Biophys 2002;403:209–18.
[23] Sarna S, Bhola RK. Toxicol Int 2007;14(1):83–7.
[24] Liu ZC, Zhou CH, Xie RG. Chin Chem Lett 1997;8(5):387–8.
[25] Blasig A, Tang J, Hu X, Tan SP, Shen Y, Radosz M. Ind Eng Chem Res 2007;46:5542–7.
[26] Evans KO. Colloid Surface Physicochem Eng Aspect 2006;274:11–7.
[27] Cho MS, Seo HJ, Nam JD, Choi HR, Koo JC, Lee Y. Smart Mater Struct 2007;16:S237–42.
[28] Durant GJ, Ganellin CR, Parsons ME. J Med Chem 1975;18(9):905–9.

[29] He X, Chan TH. Synthesis; 2006:1645–51.
[30] Frade RFM, Rosatella AA, Marques CS, Branco LC, Kulkarni PS, Mateus NMM, et al. Green Chem 2009;11:1660–5.
[31] Zhang C, Ding Z, Suhaimi NM, Kng YL, Zhang Y, Zhuo L. A class of imidazolium salts is anti-oxidative and anti-fibrotic in hepatic stellate cells. Free Radic Res 2009;43(10):899–912. First published on: 07 August 2009 (iFirst).
[32] Gava B, Zorzet S, Spessotto P, Cocchietto M, Sava G. JPET 2006;317(1):284–91.
[33] Dupont J, Suarez PAZ. Phys Chem Chem Phys 2006;8:2441–52.
[34] Welton T. Coord Chem Rev 2004;248:2459–77.
[35] Welton T. Chem Rev 1999;99:2071–83.
[36] Wasserscheid P, Keim W. Angew Chem Int Ed 2000;39:3773–89.
[37] Dupont J, de Souza RF, Suarez PAZ. Chem Rev 2002;102:3667–91.
[38] Cang H, Li J, Fayer MD. J Chem Phys 2003;119(34):13017–23.
[39] Beste Y, Eggersmann M, Schoenmakers H. Chem Ing Tech 2005;77 (11):1800–8.
[40] Amyes TL, Diver ST, Richard JP, Rivas FM, Toth KJ. Am Chem Soc 2004;126:4366–74.
[41] Arduengo AJ. Acc Chem Res 1999;32:913–21.
[42] Aggarwal VK, Emme I, Mereu A. Chem Comm; 2002:1612–3.
[43] Xu LJ, Chen WP, Xiao JL. Organometallics 2000;19:1123–7.
[44] McLachlan F, Mathews CJ, Smith PJ, Welton T. Organometallics 2003;22:5350–7.
[45] Hasan M, Kozhevnikov IV, Siddiqui MRH, Femoni C, Steiner A, Winterton N. Inorg Chem 2001;40:795–800.
[46] Oxley JD, Prozorov T, Suslick KS. J Am Chem Soc 2003;125:11138–9.
[47] Dullius JEL, Suarez PAZ, Einloft S, de Souza RF, Dupont J, Fischer J, et al. Organometallics 1998;17:815–9.
[48] Gao SY, Zhang HJ, Wang XM, Mai WP, Peng CY, Ge LH. Nanotechnology 2005;16:1234–7.
[49] Huang J, Jiang T, Han BX, Wu WZ, Liu ZM, Xie ZL, et al. Catal Lett 2005;103:59–62.
[50] Tatumi R, Fujihara H. Chem Comm; 2005:83–5.
[51] Lee BS, Lee S. Bull Korean Chem Soc 2004;25:1531–7.
[52] Mu XD, Evans DG, Kou YA. Catal Lett 2004;97:151–4.
[53] Wei GT, Sang Z, Lee CY, Yang HY, Wang CRC. J Am Chem Soc 2004;126:5036–7.
[54] Kim KS, Demberelnyamba D, Lee H. Langmuir 2004;20:556–60.
[55] Lee BS, Chi YS, Lee JK, Choi IS, Song CE, Namgoong SK, et al. J Am Chem Soc 2004;126:480–1.
[56] Huang J, Jiang T, Han BX, Gao HX, Chang YH, Zhao GY, et al. Chem Comm 2003;1:1654–5.
[57] Zhao DB, Fei ZF, Scopelliti R, Dyson PJ. Inorg Chem 2004;43:2197–205.
[58] Mu XD, Meng JQ, Li ZC, Kou YJ. Am Chem Soc 2005;127:9694–5.
[59] Binnemans K. Chem Rev 2005;105:4148–204.
[60] Bowlas CJ, Bruce DW, Seddon KR. Chem Comm 1996;1:1625–6.
[61] Kazarian SG, Briscoe BJ, Welton T. Chem Comm 2000;1:2047–8.
[62] Ott LS, Cline ML, Deetlefs M, Seddon KR, Finke RG. J Am Chem Soc 2005;127:5758–9.
[63] Bacciu D, Cavell KJ, Fallis IA, Ooi L-L. Angew Chem Int Ed 2005;44:5282–4.
[64] Mathews CJ, Smith PJ, Welton T, White AJP, Williams DJ. Organometallics 2001;20:3848–50.
[65] Fonseca GS, Umpierre AP, Fichtner PFP, Teixeira SR, Dupont J. Chem Eur J 2003;9:3263–9.
[66] Dupont J, Fonseca GS, Umpierre AP, Fichtner PFP, Teixeira SR. J Am Chem Soc 2002;124:4228–9.
[67] Yu B, Zhou F, Wang C, Liu W. Eur Polym J 2007;43:2699–707.
[68] Shinohara H, Shibata H, Wöhrle D, Nishide H. Macromol Rapid Comm 2005;26:467–70.
[69] Eisenberg A, Hird B, Moore RB. Macromolecules 1990;23:4098–107.
[70] Eisenberg A, King M. Ion-containing polymers. New York: Academic Press; 1977.
[71] Eisenberg A, Kim JS. Introduction to ionomers. New York: John Wiley & Sons, Inc.; 1998.
[72] Litschauer M, Peterlik H, Neouze M-AJ. Phys Chem C 2009;113:6547–52.
[73] Batra D, Seifert S, Varela LM, Liu ACY, Firestone MA. Adv Funct Mater 2007;17:1279–87.
[74] Baird EE, Dervan PB. J Am Chem Soc 1996;118:6141–6.
[75] Matsumi N, Sugai K, Miyake M, Ohno H. Macromolecules 2006;39:6924–7.
[76] Williams SR, Cruz DS, Winey KI, Long TE. Ionene segmented block copolymers containing imidazolium cations: structure-property relationships as a function of hard segment content, Polymer, Submited for publication.
[77] Williams SR, Long TE. Prog Polym Sci 2009;34(8):762–82.
[78] Sharlene R. Williams. Influence of electrostatic interactions and hydrogen bonding on the thermal and mechanical properties of step-growth polymers, Ph.D. thesis, Virginia Tech (Blacksburg); 2008.
[79] Beer PD, Sambrook MR, Curiel D. The Royal Society of Chemistry. Chem Comm; 2006:2105–17.
[80] Nakajima H, Ohno H. Polymer 2005;46:11499–504.
[81] Narita A, Shibayama W, Matsumi N, Ohno H. Polym Bull 2006;57:109–14.
[82] Marwanta E, Mizumo T, Ohno H. Solid State Ionics 2007;178:227–32.
[83] Kamplain JW, Bielawski CW. Chem Comm; 2006:1727–9.
[84] Tennyson AG, Kamplain JW, Bielawski CW. The Royal Society of Chemistry. Chem Comm; 2009:2124–6.
[85] Bianchi A, Bowman-James K, Garcia- Espana E, editors. Supramolecular chemistry of anions. New York: Wiley-VCH; 1997.
[86] Yoon J, Kim SK, Singh NJ, Kim KS. The Royal Society of chemistry. Chem Soc Rev 2006;35:355–60.
[87] Suzuki K, Yamaguchi M, Hotta S, Tanabe N, Yanagida SJ. Photochem Photobio A: Chem 2004;164:81–5.
[88] Li F, Cheng F, Shi J, Cai F, Liang M, Chen JJ. Power Sourc 2007;165:911–5.
[89] Ramirez SM, Layman JM, Bissel P, Long TE. Ring-opening polymerization of imidazole epoxides for the synthesis of imidazole-substituted Poly(ethylene oxides). Macromolecules 2009;42(21):8010–2.

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