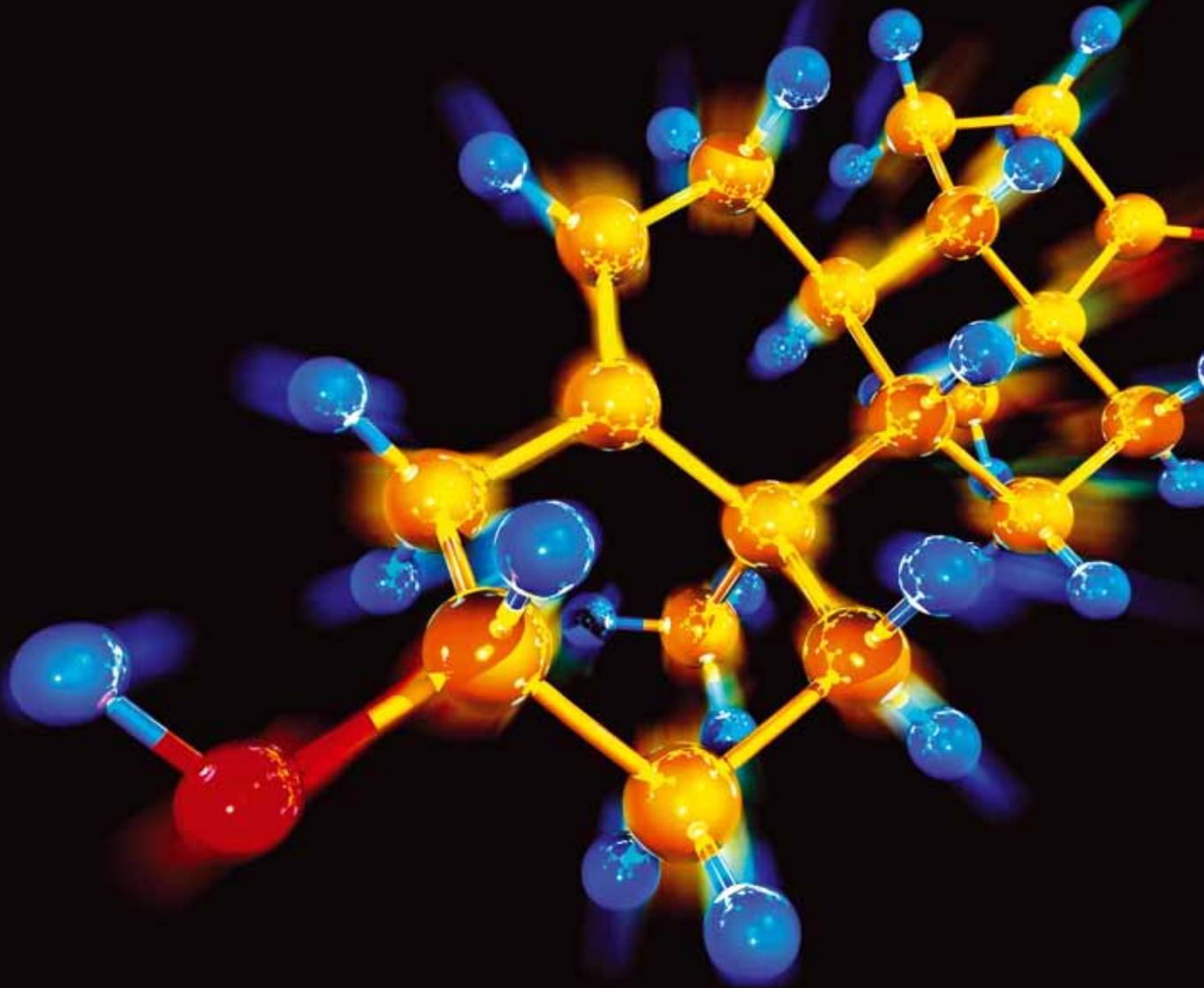


# Ionic Liquids: Green Solvents for Chemical Processing

Guest Editors: Antonia Pérez de los Ríos, Angel Irabien, Frank Hollmann, and Francisco José Hernández Fernández





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## Editorial

# Ionic Liquids: Green Solvents for Chemical Processing

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Ionic liquids are organic salts, usually consisting of an organic cation and a polyatomic inorganic anion, which are liquid under 100°C. The most relevant properties of ionic liquids are their almost negligible vapour pressure. Furthermore, their physical and chemical properties can be fine-tuned by the adequate selection of the cation and anion constituents. Ionic liquids have been recognized as environmental benign alternative to volatile organic solvents. Application of ionic liquids in chemical processes has blossomed within the last decade. Indeed, these media have been used in replacement of volatile organic solvents in a wide variety of chemical processes, such as separation and purification, and reaction media in biochemical, and chemical catalysis. This special issue focuses on these topics providing a state-of-the-art overview of new paradigms and challenges in research on ionic liquids as green solvents for chemical processes and highlights the importance of this topic.

In the call for papers, we invited contributions covering all topics in the area, including progress on developing new ionic liquids for use in chemical synthesis and catalysis and recent advances in separation processes using ionic liquids. All contributions were peer-reviewed according to the usual high standards of this journal. Our thanks go to highly qualified and thorough referees that helped us accept seven papers. They greatly contributed to the high quality of the final manuscripts.

The contributions could be grouped into two main research fields where four papers are related to the use of ionic

liquid as reaction media and/or catalyst in chemical processes three papers are oriented towards the use of these new solvents on separation processes, specifically as extraction agent in liquid-liquid separations and as liquid phase in supported liquid membranes. In the following, a brief overview and summary of the individual contributions are given.

The first contribution in this issue from V. Srivastava (NIIT University, India) is entitled “*ionic-liquid-mediated MacMillan’s catalyst for Diels-Alder reaction.*” A modified and improved protocol for MacMillan’s imidazolidinone catalyst for Diels-Alder reaction has been developed using ionic liquid as reaction media. This new protocol allowed to successfully obtain enantiomerically enriched Diels-Alder adducts with high yields and selectivities. The main features of this reaction are as follows (i) the operational simplicity of the procedure, (ii) the cycloaddition adducts were obtained in good yield and selectivities for various dienes with dienophiles resulting in good yields and high selectivity, (iii) obtaining the cycloaddition adduct with low catalyst loading, (iv) the catalyst can be recycled up to six cycles with comparable yields and selectivities, and (v) the protocol was found active in the synthesis of a tedious steroid molecule.

The paper by S. Sajjadifar et al. (Payame Noor University, Iran), which deals with the use of ionic liquid as catalyst in chemical processes, is entitled “*1-Methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride as a new and green ionic liquid catalyst for one-pot synthesis of dihydropyrimidinones under solvent-free condition.*” These authors

have investigated the use of a Bronsted acidic ionic liquid, 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride, as an inexpensive, easy-to-handle, noncorrosive, and environmentally benign catalyst for the Biginelli reaction from an aldehyde, a  $\beta$ -dicarbonyl, and urea or thiourea. The advantages of the developed procedure are simplicity of operation, very short reaction times compared with other procedures for the preparation of dihydropyrimidinones derivatives, and the high yields of products. Furthermore, the catalyst can be easily recyclable after removing starting materials and water.

The paper "*The zwitterionic imidazolium salt: first used for synthesis of 4-arylidene-2-phenyl-5(4H)-oxazolones under solvent-free conditions*" by B. Zhou and W. Chen (Zhejiang Sci-Tech University, China) is another example of the successful use of ionic liquid as catalyst. A new imidazole-based zwitterionic-type molten salt was developed and used as catalyst for the synthesis of 4-arylidene-2-phenyl-5(4H)-oxazolones, which are very important intermediates for the synthesis of a variety of bioactive molecules and fine chemicals, through the Erlenmeyer reaction under solvent-free conditions. The nonhazardous experimental conditions, ease of reaction, short reaction times, high yields, and metal-free catalyst are the notable advantages of this procedure.

In the paper entitled "*Cycloaddition reaction of carbon dioxide to epoxides catalyzed by polymer-supported quaternary phosphonium salts*" the authors Y. Xiong et al. (Northwest Normal University, China) developed new polymer-supported quaternary phosphonium salts (PS-QPS) to be evaluated as catalyst for cyclic carbonates synthesis via the cycloaddition of epoxides with  $\text{CO}_2$ . The results testified that high yields and excellent selectivity can be achieved using PS-QPS on the assayed conditions (5 MPa  $\text{CO}_2$ , 150°C in 6 h). In addition, the catalyst can be easily separated from the products and reused for up to five times without considerable decrease in the yield of cyclic carbonate.

The first contribution presented in this special issue in the field of the use of ionic liquid in separation processes is from Y. F. Li et al. (Peking University, China) with the title "*Partitioning of cephalexin in ionic liquid aqueous two-phase system composed of 1-butyl-3-methylimidazolium tetrafluoroborate and  $\text{ZnSO}_4$* ." In this paper, an ionic liquid aqueous two-phase system (ILATPS) was applied in the extraction and separation of an hydrosoluble antibiotic, cephalexin (CEX). They found that the distribution of CEX in the ILATPS was influenced by the volume of  $[\text{bmim}][\text{BF}_4]$ , the concentration of  $\text{ZnSO}_4$ , temperature, pH, and the volume of  $\text{ZnSO}_4$  solution. High extraction efficiencies (>92%) were reached using this approach.

X. Sun et al. (Mudanjiang Normal University, China) contribute to this issue of the journal with their paper "*Ultrasonic-assisted extraction of procyanidins using ionic liquid solution from *Larix gmelinii* bark*." They propose a novel extracting method for procyanidins from *L. gmelinii* bark based on the use of ionic liquids in ultrasound-assisted extraction. The results indicated that the characteristics of anions had remarkable effects on the extraction efficiency of procyanidins. The optimum conditions for the extraction were as follows:  $[\text{bmim}][\text{Br}]$  concentration 1.25 M, soak time

3 h, solid-liquid ratio 1:10, ultrasonic power 150 W, and ultrasonic time 30 min. Relative to other methods, the proposed approach provided higher extraction efficiency and obviously reduced energy-consumption time. The method may also prove useful in the development of energy saving and environmentally friendly extraction methods for procyanidins from other plant materials.

The last contribution in this special issue is from I. Cichowska-Kopczyńska et al. (Gdansk University of Technology, Poland) and entitled "*Influence of ionic liquid structure on supported ionic liquid membranes effectiveness in carbon dioxide/methane separation*." This paper evaluates the potential application of imidazolium ionic liquids containing alkyl fluoride anions (bis (trifluoromethylsulfonyl) imide and trifluoromethanesulfonate) immobilized in polymeric supports (supported ionic liquid membranes) in  $\text{CO}_2$  separation from gaseous streams. Authors found that the assayed supported ionic liquid membranes were stable, especially when using polypropylene support. The pure gas permeation results showed that the increase in alkyl chain length and therefore increase in viscosity of ionic liquid cause the decrease in permeation values. Furthermore, lower permeability was observed for trifluoromethanesulfonate anion, mainly due to higher viscosity and lower solubility of carbon dioxide. It is worthy to highlight that the SILMs used in this study were highly  $\text{CO}_2$  selective in  $\text{CO}_2/\text{CH}_4$  system which indicated the possibility of SILMs application in selective separation of carbon dioxide, especially from gas mixtures containing methane such as biogas streams.

The collection of works in this special issue constitutes one more step forward in the race for the development of desired, greener, more sustainable chemical processes in which the ionic liquids have demonstrated to be very promising green solvents. We hope that you find these papers interesting and wish you much success in your research in the field of ionic liquids as green solvents for chemical processing.

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Angel Irabien

Frank Hollmann

Francisco José Hernández Fernández

## Research Article

# Influence of Ionic Liquid Structure on Supported Ionic Liquid Membranes Effectiveness in Carbon Dioxide/Methane Separation

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This paper indicates the possibility of application of imidazolium ionic liquids immobilized in polymeric supports—supported ionic liquid membranes—in CO<sub>2</sub> separation from gaseous streams (e.g., biogas). Imidazolium salts containing alkyl fluoride anions, bis(trifluoromethylsulfonyl)imide and trifluoromethanesulfonate, selectively separating CO<sub>2</sub> were used. The permeability of CO<sub>2</sub> through membranes was investigated under gas pressure of 30 kPa and temperature range 283–298 K. Permeability values occurred to be higher for ionic liquids containing bis(trifluoromethylsulfonyl)imide anion. Moreover, CO<sub>2</sub> permeability exhibited an increase with increasing temperature for all investigated systems. Stability of supported ionic liquid membranes was studied. In total, polypropylene membrane revealed the best properties, mechanical stability and observed wettability of this support were better than for polyamide and polyvinylidene fluoride ones. Polyethersulfone supports showed similar contact angles; however, its mechanical stability was significantly lower. Obtained results allowed to evaluate the effectiveness of separation process using selected ILs and supports.

## 1. Introduction

Increasing ecological awareness and legislative changes over the last decade resulted in the development of innovative technologies for purification of exhaust gas streams and air. Due to relatively easy tuning for specific application, absorption is one of the most commonly applied methods of carbon dioxide separation. Recently, the main direction of research is finding more efficient solvents that are crucial in cost reduction of carbon dioxide capture from gas mixtures. It was demonstrated that ionic liquids (ILs) can be applied as effective solvents for such purposes [1–6]. ILs consist of large, highly asymmetric cation and small organic or inorganic anion. This structure inhibits crystallization and ensures that ILs stay in a liquid state over a wide range of temperatures. Unique properties of ionic liquids are highly desired in a physical and chemical absorption processes. They can be easily adjusted by substituting cations and

anions in their structure. Still, ionic liquids present high sorption capacity, thermal stability, and negligible vapour pressure. Application of ILs as absorbents allows avoiding contamination of outlet gas streams by absorbent vapours. This advantage gives ILs huge predominance over traditional volatile organic solvents used in purification of gaseous mixtures [7–11], especially in carbon dioxide removal. An excellent media for this purpose are imidazolium ionic liquids. These compounds selectively absorb CO<sub>2</sub> with lower coabsorption of other gases such as C<sub>2</sub>H<sub>4</sub>, C<sub>2</sub>H<sub>6</sub>, O<sub>2</sub>, and CH<sub>4</sub> [7, 12–15]. Experimental solubility values of gases in [BMIM][Tf<sub>2</sub>N] (1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide) expressed by Henry's constants  $K_H$  [MPa] at 298 K for CO<sub>2</sub>, C<sub>2</sub>H<sub>4</sub>, C<sub>2</sub>H<sub>6</sub>, O<sub>2</sub>, and CH<sub>4</sub> are 3.4, 7.0, 9.7, 173.0, and 40.3 respectively [14, 16, 17]. Moreover, gas solubility and diffusivity of the ammonium ionic liquids is of the same magnitude as of the imidazolium ones [18]. Ionic liquids are suitable solvents for upgrading

TABLE 1: Gas permeation values in 298 K described in literature.

Ionic liquid	Permeation, barrer
Carbon dioxide	
[EMIM][TfO]	920 [24]; 1171 [21, 34]
[EMIM][Tf <sub>2</sub> N]	960; 1702 [21, 34]
[EMIM][BF <sub>4</sub> ]	9699 [21, 34]
[BMIM][PF <sub>6</sub> ]	500 [35]; 544 [34]
[BMIM][Tf <sub>2</sub> N]	1344 [34]
[BMIM][BF <sub>4</sub> ]	200 [29]
[HMIM][Tf <sub>2</sub> N]	1136 [21]
Methane	
[EMIM][TfO]	63 [34]
[EMIM][Tf <sub>2</sub> N]	94; 39 [34]
[EMIM][BF <sub>4</sub> ]	44 [34]
[BMIM][PF <sub>6</sub> ]	40 [35]; 41 [34]
[BMIM][BF <sub>4</sub> ]	3 [29]
[HMIM][Tf <sub>2</sub> N]	134 [34]

biogas that can be further used in industry. Upgraded biogas can be injected in the gas grid or used as vehicle fuel and eventually for electricity and heat production. Apart from 50 to 75% of methane, biogas contains about 25–45% of carbon dioxide and some amounts of hydrogen sulphide, ammonia, nitrogen, hydrogen, carbon monoxide, and oxygen. Presence of these gases results in a lower energy content of biogas per unit volume when comparing to the natural gas and therefore removal of CO<sub>2</sub>, that significantly reduces its calorific value and increases corrosion, is required in many applications.

However, the high price of ILs and toxicity remain the limitations of their application in industrial scale. Thus, membrane processes allow reducing these issues. Ionic liquids can be embedded in pores of polymer supports where they are kept by capillary forces (supported ionic liquid membrane (SILM)). Therefore, membrane technology enables decrease of solvent consumption, and in consequence, costs of separation processes are lower [19–24]. There are several membrane technologies than can be used in CO<sub>2</sub> separation, for example, membrane contactors preventing dispersion of one phase into another [25]. There can be two kinds of contactors: parallel and cross-flow, depending on the flow direction. Cross flow contactors are considered to have some advantages over parallel contactors: higher mass transfer coefficients, lower shell-side pressure drop [26, 27]. Supported liquid membrane systems contain thin barrier of ionic liquid that enables selective permeation of CO<sub>2</sub> and H<sub>2</sub>S if present [28, 29]. SILMs became a good alternative to nonporous polymer membranes due to increased gas diffusion rate [30–32]. However, some authors find polymerizing of room temperature ionic liquids as a solution for low stability of SILMs in high operating pressures [33].

Usually, scientific publications present Henry’s constant values as the main parameter determining absorption of CO<sub>2</sub> in several types of ILs (imidazolium, ammonium, pyridinium, pyrrolidinium, and phosphonium) [2, 12, 14, 16, 17, 37–40]. However, taking into account the mechanisms

of mass transport through the liquid membranes, Henry’s constant is not the only parameter governing the possibility of solvent application in membrane separation processes. In fact, possibility of CO<sub>2</sub> capture from gas streams is determined also by the diffusion coefficient that characterises rate of transport of gas molecules through liquid membrane. From a thermodynamic point of view, separation process in liquid membrane can be described best by the diffusion coefficient formula based on solution-diffusion model (SDM) [32, 35] as follows:

$$P_i = D_i \cdot S_i, \quad (1)$$

where  $D_i$  is diffusion coefficient [m<sup>2</sup>/s], and  $S_i$  is solubility of gas  $i$  in the membrane [mol/m<sup>3</sup>·Pa], and  $P_i$  is permeation through the membrane [mol/s·m·Pa].

One has

$$P_i = \frac{J_i \cdot l}{(p_{i,f} - p_{i,p})}, \quad (2)$$

where  $J_i$  is molar diffusion flux of component  $i$  through the membrane [mol/m<sup>2</sup>s],  $l$  is thickness of the membrane [m],  $p_{i,f}$  is partial pressure of component  $i$  in the feed stream [Pa], and  $p_{i,p}$  is partial pressure of component  $i$  in permeate stream [Pa].

Table 1 presents exemplary permeation values published in the literature.

Differences between permeation values can be a result of differences in operational conditions, for example, pressure, humidity of gas streams, and purity of ionic liquids used in experiments.

Literature data suggest that as a result of good solubility of CO<sub>2</sub> and low absorption of other gases, selective absorption of CO<sub>2</sub> from biogas and exhaust gas streams is possible [41]. Carbon dioxide/methane selectivity for [EMIM][TfO] and [EMIM][Tf<sub>2</sub>N] reported in the literature is about 18.5 and 12, respectively [21, 34].

As pointed out by Zhao et al. the outlook for carbon dioxide capture is to study the low pressure transport in ionic liquids [42]. This research deals with the issue of low pressure separation of carbon dioxide from CO<sub>2</sub>/CH<sub>4</sub> gas mixtures, like for example biogas streams. As indicated previously, high selectivity of separation enables efficient biogas upgrading using ionic liquids.

## 2. Experimental

**2.1. Materials.** Supported ionic liquids membranes were prepared using selected polymeric supports: *GH Polypro* (polypropylene) (PP), *FP Vericel* (polyvinylidene fluoride) (PVDF), *Nylaflo* (polyamide) (PA), and *Supor* (polyether-sulphone) (PES), (Pall, Gelman Laboratory, USA). For permeation experiments PP membrane was selected in order to good wettability and low swelling as indicated in results section. Four ionic liquids were applied as a membrane phase:

1-ethyl-3-methylimidazolium  
bis(trifluoromethylsulfonyl)imide [EMIM][Tf<sub>2</sub>N],

TABLE 2: Physicochemical parameters of polymeric supports reported by producer.

Support	Density, kg/m <sup>3</sup>	Pore diameter, $\mu\text{m}$	Total porosity, %	Thickness, $\mu\text{m}$
PP	900	0.2	80	92
PVDF	1790	0.2	80	123
PA	1130	0.2	80	110
PES	1370–1510	0.2	80	148

TABLE 3: Physicochemical properties of ionic liquids used in the experiments at 298 K.

Ionic liquids	Chemical formula	Density, g/cm <sup>3*</sup>	Viscosity, mPa·s	Surface tension, mN/m
[EMIM][Tf <sub>2</sub> N]	[C <sub>6</sub> N <sub>2</sub> H <sub>11</sub> ] <sup>+</sup> [(CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> N] <sup>-</sup>	1.52	32.60	32.56
[EMIM][TfO]	[C <sub>6</sub> N <sub>2</sub> H <sub>11</sub> ] <sup>+</sup> [CF <sub>3</sub> SO <sub>3</sub> ] <sup>-</sup>	1.39	40.40	37.82
[BMIM][Tf <sub>2</sub> N]	[C <sub>8</sub> N <sub>2</sub> H <sub>15</sub> ] <sup>+</sup> [(CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> N] <sup>-</sup>	1.43	48.06	30.83
[BMIM][TfO]	[C <sub>8</sub> N <sub>2</sub> H <sub>15</sub> ] <sup>+</sup> [CF <sub>3</sub> SO <sub>3</sub> ] <sup>-</sup>	1.29	74.30	34.67

\*Data provided by producer.

1-ethyl-3-methylimidazolium trifluoromethanesulfonate [EMIM][TfO],

1-butyl-3-methylimidazolium

bis(trifluoromethylsulfonyl)imide [BMIM][Tf<sub>2</sub>N],

1-butyl-3-methylimidazolium trifluoromethanesulfonate [BMIM][TfO].

Imidazolium ionic liquids with [Tf<sub>2</sub>N] and [TfO] anions were selected, as they exhibit very good carbon dioxide absorption in comparison to [BF<sub>4</sub>], [PF<sub>6</sub>] [14, 17, 43]. All chemicals were supplied by IOLITEC, Heilbronn, Germany, with purity above 99%. In order to determine the effect of chemical structure of the ionic liquids on CO<sub>2</sub> diffusion, different alkyl chain lengths of the cations and different anions were selected.

Physical and chemical properties of polymeric supports and ionic liquids applied in experiments are presented in Tables 2 and 3.

## 2.2. Methods

**2.2.1. Viscosity, Surface Tension, and Contact Angles Measurements.** Measurements of dynamic viscosity coefficient of selected ionic liquids were conducted using Brookfield Rheometer LV III. The dependence of shear stress (Pa) on shear rate (1/s) was determined. Ionic liquids viscosity remains constant with increasing shear rates. Such linear relationship between shear stress and shear rate is related to newtonian character of the liquid. Surface tensions of selected ionic liquids were determined by the pendant drop method using Tensiometer Krüss DSA 10. Contact angles measurements were carried out using dynamic sessile drop method using Tensiometer Krüss DSA 10. Results are shown in Tables 3 and 4.

**2.2.2. Supported Ionic Liquid Membranes Preparation Procedure.** Polymer supports and ionic liquids were degassed in vacuum dryer *Vacucell 55* according to procedure described in the literature [44–46]. After degassing water

content in ionic liquids was determined using Karl-Fischer coulometric titration method with Metrohm 831 KF Coulometer: [EMIM][TfO]-0.370%, [BMIM][TfO]-0.134%, [EMIM][Tf<sub>2</sub>N]-0.001%, [BMIM][Tf<sub>2</sub>N]-0.109%. Nevertheless, ionic liquids are hygroscopic, so the water content could change during the experiments.

The literature data suggest that the small addition of water improves the performance of membrane. Carbon dioxide permeation increases when the molar fraction of water increases from 0 to 0.1. This improvement can be attributed to increased diffusivity due to the lower viscosity of ionic liquid [47].

Degassed polymeric supports were saturated with 0.1 cm<sup>3</sup> of ionic liquids per 1.0 cm<sup>2</sup> of support surface. The excess of ionic liquid was removed from membrane surface using blotting paper until weight of immobilized membrane was stable. The procedure was repeated three times in order to provide complete pores saturation.

**2.2.3. Determination of Supports Swelling.** Swelling of supports was determined on the basis of supports thickness. Thickness was determined by optical method using epifluorescent microscope L3001 equipped with digital camera Canon Power Shot A650 SI. Membrane was placed in glass holder in Z direction according to the procedure described in the literature [48]. In previous work membrane swelling after 24 hours was determined. In present paper, in order to evaluate the time period of swelling effect, data obtained after 72 and 120 hours are presented.

**2.2.4. Evaluation of SILMs Stability.** Mechanical resistance of membrane systems on pressure difference over the membrane was investigated in laboratory test unit presented in Figure 1. Both sides of the chamber were evacuated using vacuum pump, and inert gas was released to the feed side at a rate of 50 Pa/s. Pressure difference was recorded using pressure sensors MPX 5100DP and software using Glanguage. Experiments were conducted in 283, 288, and 298 K.

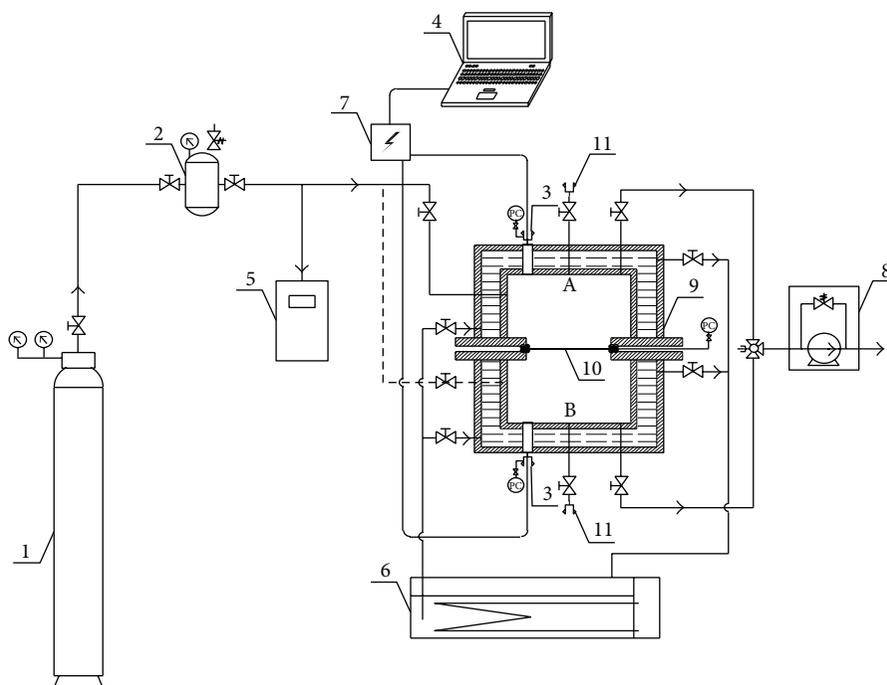


FIGURE 1: Diagram of the laboratory unit for the determination of  $\text{CO}_2/\text{CH}_4$  permeation: 1:  $\text{CO}_2/\text{CH}_4$  gas container, 2: gas sample container, 3: pressure sensor, 4: computer, 5:  $\text{CO}_2$  analyser, 6: thermostat, 7: A/D converter, 8: vacuum pump, 9: chamber, 10: SILM, and 11: valves.

**2.2.5. Determination of Carbon Dioxide/Methane Permeation.** Permeation was determined using laboratory unit shown in Figure 1. Polymeric support saturated with ionic liquid (10) was placed in a stainless steel chamber (9), consisting of two parts: upper (feed side) and bottom (permeate side). The chamber was equipped with heating jacket coupled with thermostat (6). The experiments were carried out in 283, 288, and 298 K with 0.1 K accuracy. Both sides of the chamber were equipped with electronic temperature sensors and connected to vacuum oil pump (8). Gas container (1) was attached through differential pressure regulator with thermostatic gas sample container (2) connected to the feed part of the chamber. Pressure sensor signal (*MPX 5100 DP*) was transmitted to the A/D converter (7) and was recorded with software using G-language (4). The  $\text{CO}_2$  concentration in gas sample container was measured using IR analyser (5) in order to ensure that there are no other gases present in the container apart from carbon dioxide.

Experiments were carried out as the following:

- (i) obtaining vacuum in feed and permeate sides (to remove  $\text{CO}_2$ ,  $\text{O}_2$ ,  $\text{N}_2$ , and other gases),
- (ii) filling gas sampler (2) with  $\text{CO}_2/\text{CH}_4$ ,
- (iii) obtaining desirable temperature in the chamber and gas sampler containing  $\text{CO}_2/\text{CH}_4$ ,
- (iv) filling the feed side of the chamber with  $\text{CO}_2$  from gas sample container at a rate of 50 Pa/s, to obtain 30 kPa pressure difference between feed and permeate side. The pressure of 30 kPa was the maximum pressure that did not cause SILM deformation.

The drop of pressure in feed chamber and increase of pressure in permeate chamber were determined with differential pressure sensor during the experiment.

Permeation was determined on the basis of pressure difference between the feed and permeate side in time period when the pressure drop was linear.

Figure 2 presents the linear approximation of pressure difference included in (2).

Thickness of the membrane was determined before each measurement.

Application of freshly prepared SILM membrane for each experiment allowed to use the same volume of feed stream and permeate stream in every single experiment and to eliminate necessity of determination of the  $\text{CO}_2$  amount already dissolved in the ionic liquid.

### 3. Results and Discussion

**3.1. Determination of Supports Swelling and Wettability.** We have previously reported data on swelling of the membrane after 24 hours from immobilization procedure [36]. All the investigated supports showed higher thickness after immobilization with ionic liquid.

In present paper, data on thickness after 2, 72, and 120 hours from saturation are presented. The initial thickness of the membranes is as follows: PP  $75 \pm 1$ , PA  $115 \pm 1$ , PES  $118 \pm 1$ , and PVDF  $160 \pm 1$ . Considering data presented in Figure 3, rapid increase of thickness is observed immediately after impregnation, further differences are rather less distinct; however, the trend is preserved. Polyamide support shows similar thickness for all ionic liquids used in this study, the

TABLE 4: Wettability of polymeric supports by ionic liquids determined by sessile drop method at 298 K [36].

Ionic liquid	Support	Advancing angle $\theta_a$ , deg	Receding angle $\theta_r$ , deg	Hysteresis $\theta_a - \theta_r$ , deg
[EMIM][Tf <sub>2</sub> N]	PES	16.6 ± 0.2	9.6 ± 0.2	7.0
	PVDF	12.5 ± 0.7	7.4 ± 0.1	5.1
	PA	10.3 ± 0.5	6.8 ± 0.6	3.5
	PP	12.3 ± 0.5	7.8 ± 0.6	4.5
[EMIM][TfO]	PES	14.5 ± 0.6	8.3 ± 0.2	6.2
	PVDF	15.5 ± 0.6	8.4 ± 0.2	7.1
	PA	14.2 ± 0.3	8.1 ± 0.2	6.1
	PP	11.8 ± 0.9	5.6 ± 0.7	6.2
[BMIM][Tf <sub>2</sub> N]	PES	16.9 ± 0.2	8.2 ± 0.2	8.7
	PVDF	19.2 ± 0.5	10.9 ± 0.5	8.3
	PA	10.7 ± 0.4	8.4 ± 0.3	2.3
	PP	13.9 ± 0.4	8.0 ± 0.3	5.9
[BMIM][TfO]	PES	15.5 ± 0.2	8.1 ± 0.2	7.4
	PVDF	18.3 ± 0.6	10.4 ± 0.7	7.9
	PA	8.1 ± 0.3	6.6 ± 0.1	1.5
	PP	10.5 ± 0.3	8.8 ± 0.5	1.7

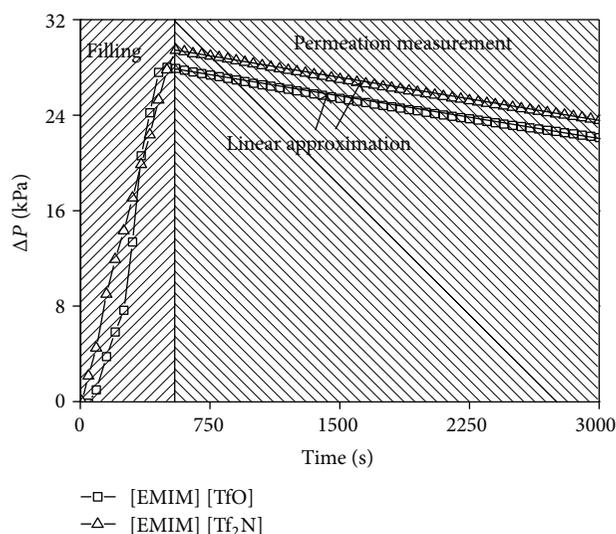


FIGURE 2: Linear approximation of pressure difference.

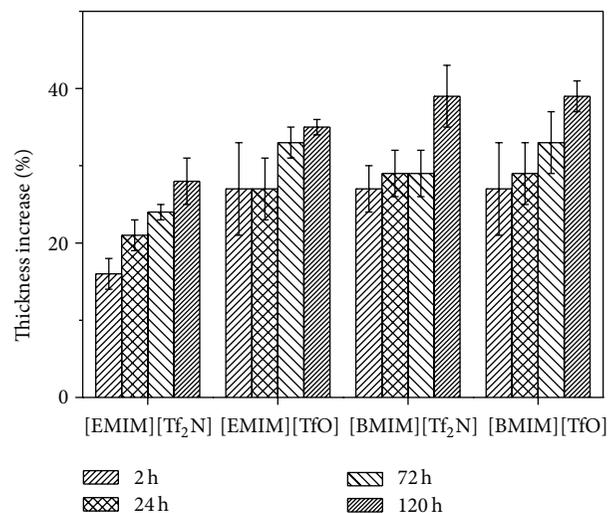


FIGURE 3: Increase of polypropylene membrane thickness.

rate of swelling is the lowest, and it corresponds to incomplete pores saturation with the liquid, that was calculated on the basis of ratio of the real mass of IL embedded in the support pores and the theoretical value of the maximum amount of IL possible to immobilize.

Swelling of polymeric membranes can affect mechanical stability of the supports decreasing the maximum transmembrane pressure possible to apply without causing membrane damage.

The rate of swelling for all ionic liquids used in the study is similar and stays with correlation to wetting of the supports. All the values of contact angles calculated from sessile drop measurements (Table 4) were below 20 deg.,

therefore all the examined ionic liquids are suitable for perfect wetting of supports. The best wettability was observed for PA membrane, successively for PP, PVDF, and PES; however, the differences are not significant.

According to Young equation assumptions, equilibrium contact angle does not change when changing the drop volume. Supports examined in this study do not meet Young equation foundations, the drop is in the metastable state, and the hysteresis is observed. There are two components of the hysteresis value, the first one is the thermodynamic hysteresis dependent on the surface roughness and heterogeneity, whereas the second one is the dynamic hysteresis that is connected to chemical interactions of liquid and solid,

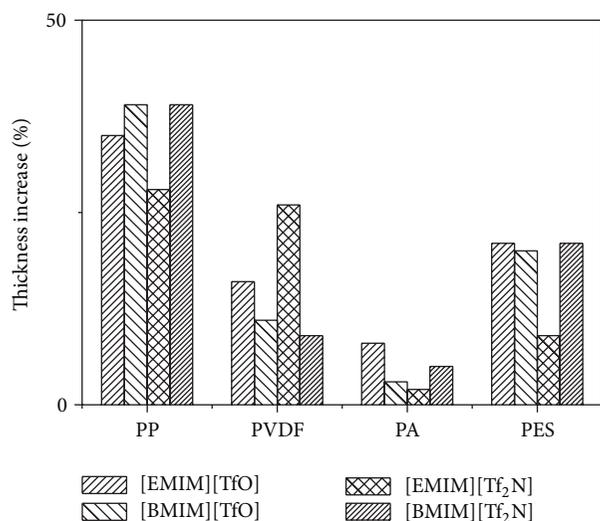


FIGURE 4: Increase of thickness of different supports saturated with ionic liquids after 120 hours.

penetration of liquid into polymer pores, and the ability of atoms or functional groups to change its positions.

The first component is not affected by the time of solid-liquid drop contact, whereas dynamic hysteresis is, and moreover is dependent on the properties of polymer and ionic liquid.

Taking into account swelling of the supports, it is observed that the polypropylene membrane gains almost the same thickness immediately after impregnation for all ionic liquids used in the study, and it can be assumed that the hysteresis is dependent only on the surface roughness and heterogeneity. Further changes in thickness of the supports are connected to the liquid penetration into the pores and free space between polymer molecules and reorientation of functional groups of ionic liquids, so the particles in the ionic liquid-polymer interface reach the minimum of free interface energy. Polypropylene supports gain about 30–40% of thickness and yet PA ones gain only about 4% (Figure 4).

**3.2. Determination of Mechanical Stability.** The mechanical stability of investigated supports was determined in order to check the potential of technological application. Figure 5 presents maximum transmembrane pressure not causing polypropylene support damage. Supported ionic liquid membranes based on polypropylene support present the highest mechanical stability for operating pressures between 40 and 50 kPa. Pressure changes in course of experiment are shown in Figure 6. The peak at the curve is a result of pushing the solvent out of the pores of the support, and the gas leakage is observed. Further increase of feed stream pressure applied over the membrane leads to the polypropylene support damage, whereas for other SILMs the transmembrane pressure possible to apply without support degradation is lower than pressure required to push the impregnating liquid out of the pores. The highest pressure difference across the membrane obtained during the experiments reached 59 kPa.

Data presented in Table 5 suggest that polypropylene membrane is more stable in lower temperatures. Higher stability for PP-[EMIM][TfO] membrane stays in correlation with swelling of the membrane. Swelling rate of the PP membrane is lower for [EMIM][TfO] than for [EMIM][Tf<sub>2</sub>N]. Structure changes of PP impregnated with [EMIM][Tf<sub>2</sub>N] caused lower mechanical stability of this system. However, experiments conducted in higher temperatures with different ionic liquids need to be done. Polyethersulphone membrane was damaged even if minimum pressure was applied.

In order to determine the impact of cation structure on stability of the system, polypropylene membrane was also impregnated with ionic liquids based on 1-butyl-3-methylimidazolium cation. For PP-based systems, maximum pressure difference between feed and permeate side was higher when using [TfO] based ionic liquids: about 60 kPa for [EMIM][TfO] and 48 kPa for [BMIM][TfO], than for systems using [Tf<sub>2</sub>N] ionic liquids as a membrane phase: 56 kPa for [EMIM][Tf<sub>2</sub>N] and 46 kPa for [BMIM][Tf<sub>2</sub>N]. The differences are not significant; however, when related to all examined temperatures, in total, membranes using ionic liquids based on [TfO] anion are slightly more stable, nevertheless it stays with a disagreement to the swelling data. However, it is likely that [TfO] anion-based ionic liquids make polypropylene more elastic enhancing the pressure resistance. The membrane is then deformed under the pressure before cracking.

The cation structure also affects mechanical properties. It can be seen that the longer hydrocarbon chain in cation structure is, the more disruptions in membrane structure occur, and the lower the mechanical stability is. Ionic liquid penetrates into the support pores and between polymer particles and fibers reorientating its structure to energetically favorable position. The longer alkyl chain length, the greater space is occupied with the ionic liquid, and the greater support expansion is observed.

Obtained results suggest that it is possible to use such SILMs without any additional mechanical supports in ventilation systems that reveal only slight pressure fluctuations. Moreover, applying SILMs to improve biogas quality directly in outlets of fermentation reactors without gas compression would also bring some profits. In many cases for the proper work of electric generators it is necessary to increase the methane content in biogas. That is why the application of SILMs is considered to be a promising perspective, especially when comparing to other methods requiring pressure increasing and regeneration of absorbent.

**3.3. Determination of Carbon Dioxide and Methane Permeation.** Permeability of the supported ionic liquid membranes at different temperatures is presented in Table 6. It can be seen that for each SILM system permeability increases with the increase of temperature.

Carbon dioxide permeability of the PP membrane-[EMIM][TfO] system increases from 636 to 1076 barrers, as the temperature increases from 283 to 298 K and from 749 to 1888 barrers for PP membrane-[EMIM][Tf<sub>2</sub>N] system. Temperature increase causes an increase of ions activity and

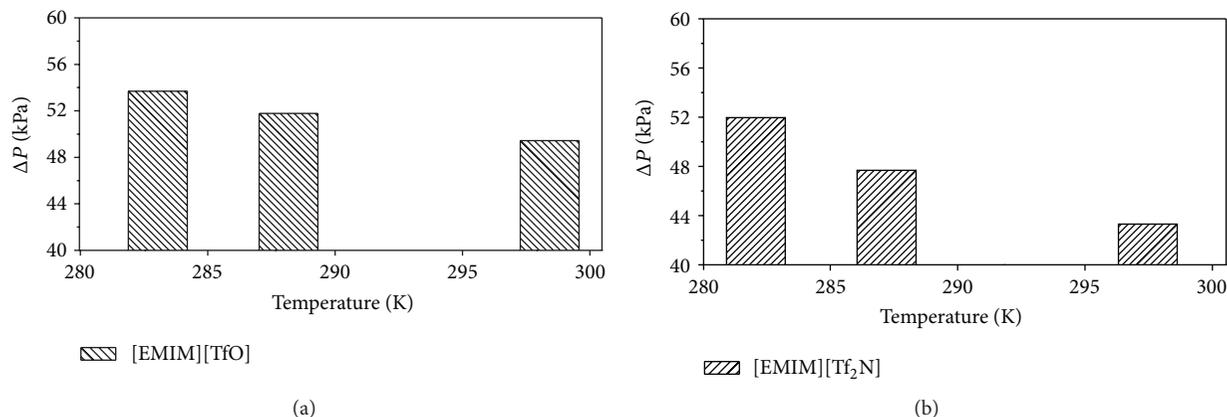


FIGURE 5: Maximum transmembrane pressure obtained for PP support in different temperatures.

TABLE 5: Mechanical stability of supports.

Membrane	Ionic liquid	Maximum pressure difference obtained, kPa	Average pressure difference in 283 K, kPa	Average pressure difference in 288 K, kPa	Average pressure difference in 298 K, kPa
PES	[EMIM][Tf <sub>2</sub> N]	4.70	n/a	n/a	4.70 ± 0.30
	[EMIM][TfO]	5.21	n/a	n/a	5.10 ± 0.20
PVDF	[EMIM][Tf <sub>2</sub> N]	22.81	22.14 ± 1.05	21.57 ± 1.24	20.18 ± 1.53
	[EMIM][TfO]	21.82	21.10 ± 0.63	20.60 ± 0.43	20.15 ± 0.87
PA	[EMIM][Tf <sub>2</sub> N]	22.30	n/a	n/a	20.31 ± 1.21
	[EMIM][TfO]	13.42	n/a	n/a	11.20 ± 0.96
PP	[EMIM][Tf <sub>2</sub> N]	55.75	51.97 ± 3.48	47.68 ± 3.06	43.31 ± 4.77
	[EMIM][TfO]	59.53	53.68 ± 1.87	51.78 ± 3.39	49.43 ± 6.23
	[BMIM][Tf <sub>2</sub> N]	47.64	46.40 ± 1.02	45.08 ± 1.73	44.59 ± 2.89
	[BMIM][TfO]	51.78	50.65 ± 1.16	48.28 ± 1.48	47.07 ± 1.00

decrease of ionic liquid viscosity and therefore an increase of CO<sub>2</sub> permeation. According to presented data it can be concluded that the longer is hydrocarbon chain in the cation structure, the lower permeability is observed. Scovazzo et al. reported similar permeability for PES support impregnated with [EMIM][Tf<sub>2</sub>N], 960 barrers at room temperature. Ilconich et al. in their study of PS membranes immobilized with [HMIM][Tf<sub>2</sub>N] reported a CO<sub>2</sub> permeability 744 barrers at 310 K and 1200 barrers at 398 K [49].

It can be concluded that choosing proper polymer support is essential for obtaining satisfactory CO<sub>2</sub> permeation. For example Baltus et al. used an inorganic (γ-alumina) support with [BMIM][Tf<sub>2</sub>N] and obtained significantly lower values of permeation-70 barrers [4].

Methane permeation values stay in agreement with literature data. They are significantly lower than carbon dioxide permeation values. Selectivity obtained by dividing the permeabilities of two pure gases is about 16 for [EMIM][TfO] and 17 for [EMIM][Tf<sub>2</sub>N].

## 4. Conclusions

It has been shown that the supported ionic liquid membranes prepared with ionic liquids based on the 1-alkyl-3-methylimidazolium cation are stable, especially when using polypropylene support. The effect of alkyl chain length in IL structure on the permeability was studied. The pure gas permeation results have shown that the increase in alkyl chain length and therefore increase in viscosity of ionic liquid cause the decrease in permeation values. The effect of using different ILs anions on the permeability of carbon dioxide was also evaluated, and lower permeability was observed for [TfO] anion, mainly due to higher viscosity and lower solubility of carbon dioxide. Results have also shown that the SILMs used in this study are highly CO<sub>2</sub> selective in CO<sub>2</sub>/CH<sub>4</sub> system. This fact indicated the possibility of SILMs application in selective separation of carbon dioxide, especially from gas mixtures containing methane such as biogas streams.

TABLE 6: Permeability of carbon dioxide and methane through SILMs (with PP support) at different temperatures.

Ionic liquid	Temperature, K	Permeability, barrer		Viscosity of ionic liquid, mPa·s
		Carbon dioxide	Methane	
[EMIM][Tf <sub>2</sub> N]	283	749 ± 14	n/a	56.36 ± 1.93
	288	811 ± 14	n/a	51.55 ± 1.27
	298	1888 ± 117	101 ± 1	40.40 ± 1.80
[EMIM][TfO]	283	636 ± 69	n/a	44.77 ± 0.63
	288	684 ± 31	n/a	42.26 ± 0.61
	298	1076 ± 111	60 ± 17	32.60 ± 1.07
[BMIM][Tf <sub>2</sub> N]	298	936 ± 26	77 ± 2	74.30 ± 0.71
[BMIM][TfO]	298	754 ± 33	43 ± 2	48.06 ± 1.95

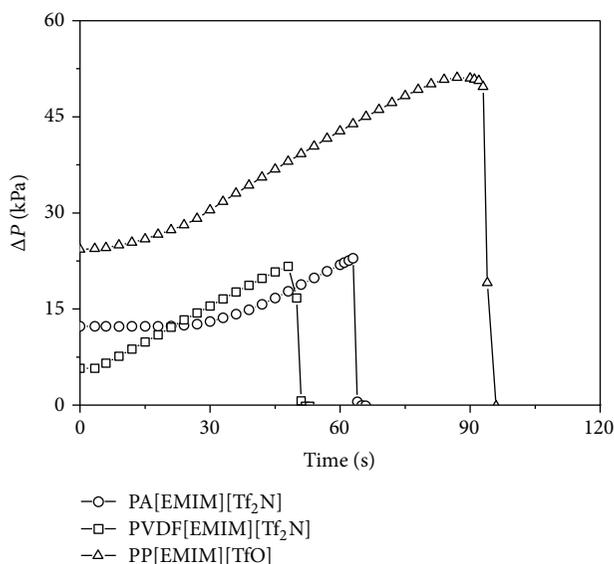


FIGURE 6: Pressure changes during stability measurements of SILMs.

SILMs systems used in this study occurred to be more stable when applying lower temperatures. When choosing proper support and type of ionic liquid, it is important to take into account properties of both. Due to interactions between them, effectiveness and lifetime of the membranes can differ significantly in connection to wettability and swelling of the support. Mechanical stability is strongly dependent on those interactions that are expressed by the rate of swelling and contact angles. Structural changes in the polymer usually result in the decrease of mechanical stability and increase of the length of permeation path. Additionally poor wetting can cause interruption of continuity of liquid membrane.

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## Research Article

# The Zwitterionic Imidazolium Salt: First Used for Synthesis of 4-Arylidene-2-phenyl-5(4H)-oxazolones under Solvent-Free Conditions

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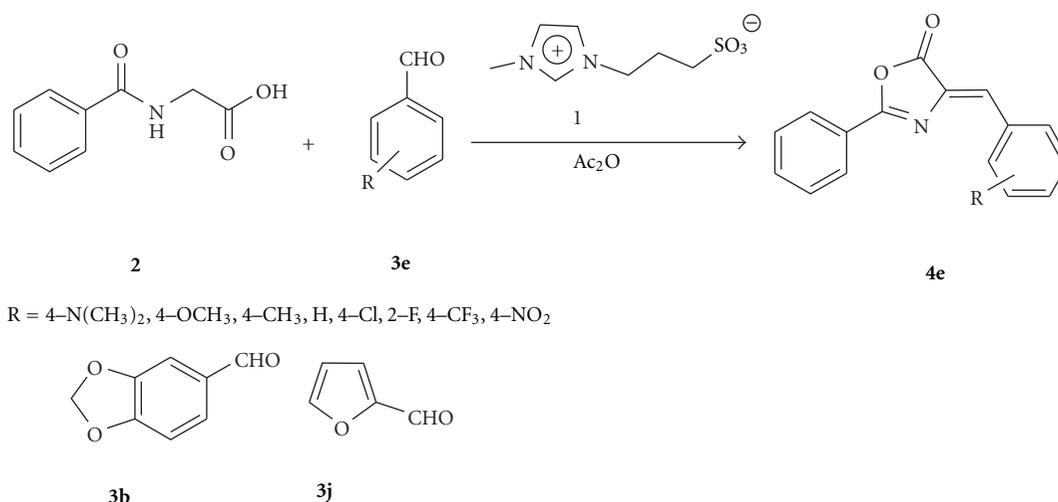
The zwitterionic imidazolium salt was prepared and characterized by <sup>1</sup>H NMR. It was first used for synthesis of azlactones via Erlenmeyer synthesis from aromatic aldehydes and hippuric acid under solvent-free conditions. It was found that aldehyde substituents play an important role in these reactions. Better conversions and therefore higher isolated yields were observed when electron-withdrawing groups (EWG-) were present in the aromatic aldehyde. Opposite results were shown when electron-donating groups (EDG-) were present in the aromatic aldehyde. However, azlactones were obtained in moderate to high yields.

## 1. Introduction

4-Arylidene-2-phenyl-5(4H)-oxazolones are very important intermediates for the synthesis of a variety of bioactive molecules, fine chemicals, and precursors of several biologically active molecules such as amino acids and peptides [1]. These compounds are especially active as anticancer [2], antitumor [3], and inhibitors of central nervous system. Besides, these compounds are unique precursors for the synthesis of amino acids, peptides [4], heterocyclic compounds [5], and biosensor [6, 7]. In fact, these precursors could be synthesized by Horner-Emmons, Heck, or Erlenmeyer-Plöchl [8] reactions followed by a complementary asymmetric hydrogenation reaction. The most common route to oxazolones involves the condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate in the presence of acetic anhydride as the dehydrating agent [9], such methodology is known as the Erlenmeyer-Plöchl reaction [1].

Since the first report on the synthesis of azlactones published in 1883, a number of catalysts have been developed in

recent years. For example, lead acetate [10], SO<sub>3</sub> in dimethylformamide [11], perchloric acid [12], polyphosphoric acid [13], carbodiimides [14], anhydrous zinc chloride [15], Bi(OAc)<sub>3</sub> [16], Bi(OTf)<sub>3</sub> [17], Ca(OAc)<sub>2</sub> [18], KF-alumina [19], Yb(OTf)<sub>3</sub> [20], POCl<sub>3</sub> [21], H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> [22], Sm [22], RuCl<sub>3</sub> [22], Al<sub>2</sub>O<sub>3</sub> [23], organic bases [1, 24], K<sub>3</sub>PO<sub>4</sub> [25], and organic-inorganic hybrid polyoxometalates [26] have been used to perform this condensation. However, some of these procedures have important drawbacks, such as the use of water-sensitive catalyst [11, 15, 19], the use of noble metal/or salts as catalysts [16, 20, 22], rigorous conditions [12, 21, 25], and the use of toxic reagents [1, 10, 12, 21, 25]. Additionally, many literatures [15–23, 26] show that the aldehydes bearing electron-donating groups (EDGs, such as -NR<sub>2</sub>, -NHR, -NH<sub>2</sub>, -OH, -OR, -OCOR, and -CH<sub>3</sub>) were more reactive than electron-withdrawing groups (EDGs, such as -NO<sub>2</sub>, -CF<sub>3</sub>, -CCl<sub>3</sub>, -CN, -COOH, -CO<sub>2</sub>R, and -F). Only few reports [1, 24, 25] show opposite results. Then, there is a need for the development of environmentally benign methods, for example solvent-free condition, nontoxic reagents, mild reaction, simpler workup, and EDGs-active.



SCHEME 1: The zwitterionic imidazolium salt (1) catalyzed the Erlenmeyer reaction.

Recently, Rostami has reported a new organic-inorganic hybrid polyoxometalates for the catalytic Erlenmeyer-Plöchl reaction involved using  $[\text{bmim}]_3\text{PW}_{12}\text{O}_{40}$  and  $[\text{bmim}]_4\text{W}_{10}\text{O}_{32}$  as catalysts [26]. They found that the ion identity has an important impact on its property, and the introduction of [bmin] ion resulting more efficient than that of the others (such as  $\text{K}^+$ ). Furthermore, the using of  $\text{PW}_{12}\text{O}_{40}^{3-}$  and  $\text{W}_{10}\text{O}_{32}^{4-}$  will cause environmental problems. Besides, the aldehydes bearing electron-donating groups (EDGs) were given higher product yield and short time. Recently, zwitterionic salts have become research topic due to high ion density and high matrix mobility at ambient temperature [27]. Hajra has recently reported that zwitterionic-type molten salt may act as a bifunctional organocatalyst in the aza-Henry reaction [28] and for synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthols [29]. The imidazolium salt (1) contained [bmim] as cation and sulfonate as anion by covalent binding. According to [26], we want to know whether the introduction of sulfonate as anion instead of  $\text{PW}_{12}\text{O}_{40}^{3-}$  and  $\text{W}_{10}\text{O}_{32}^{4-}$  could impact on its catalytic property. Interested in this question and our continual research in the Erlenmeyer reaction [20], we report here the preparation, characterization, and catalytic activity of the imidazolium salt (1) in the catalyzed Erlenmeyer reaction for synthesis of azlactones under solvent-free conditions (Scheme 1).

## 2. Results and Discussion

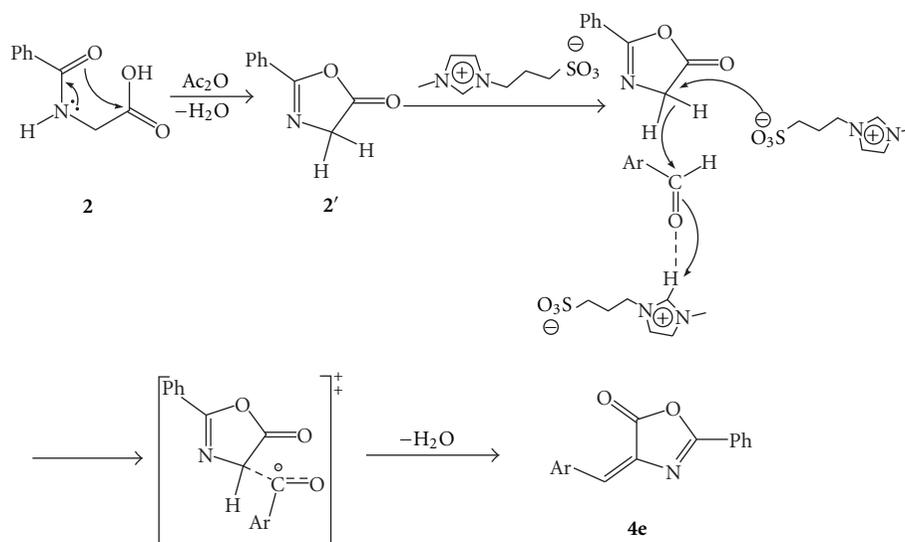
The imidazolium salt (1) was synthesized [27] and characterized by  $^1\text{H}$  NMR. In order to evaluate the catalytic activity of sulfonate, several sulfonates such as imidazolium salt (1), methanesulfonic acid, and sulfamic acid were tested in the Erlenmeyer reaction. The results are reported in Table 1. It was found that imidazolium salt (1) (Table 1, entry 1) provided azlactone 4e in the highest isolated yield in very simple procedure and was therefore selected for further study.

TABLE 1: Evaluation of several sulfonates in the Erlenmeyer reaction.

Entry	Catalyst	Reaction temperature (°C)	Reaction time (h)	Isolated yields (%) <sup>a</sup>
1	Imidazolium salt (1)	60	4	76
2	$\text{CH}_3\text{SO}_3\text{H}$	60	4	16
3	$\text{NH}_2\text{SO}_3\text{H}$	60	4	7

<sup>a</sup>Based on benzaldehyde; isolated yields based on benzaldehyde; 5 mmol benzaldehyde, 5.5 mmol hippuric acid, 10 mmol% catalyst, and 15 mmol acetic anhydride were used.

The overall process defined as the Erlenmeyer reaction was initially studied using benzaldehyde 3e as the substrate (Table 2). As shown in Table 2, different conditions have been conducted such as the amount catalyst, temperature, and reaction time. The amounts of textbf1 were tested, and it was found that 5 mmol% of 1 was enough to accomplish the reaction (Table 2, entries 2–5) when 10 mmol% of stoichiometric amount were required as previously reported. Increasing the amount of catalyst did not obviously improve the yield. Besides, 2-phenyloxazol-5-one was found as by-product when used without catalyst in the reaction which was in accordance with [23]. 2-phenyloxazol-5-one was proved as important intermediate in the Erlenmeyer reaction. Similarly, reaction temperature and time were also investigated. The isolated yield was low (15%, Table 2, entry 6) as the condensation of hippuric acid to 2-phenyloxazol-5-one needs high temperature. However, some unknown by-products were formed when reaction temperature heated up to reflux temperature and caused lower yield than the yield in 60 °C. In the reflux temperature, heavy slurry was found causing initial reactor agitation problems and an extended process reaction time [24]. It was found that four hours seem to be the optimum reaction time as shown in Table 2 (entries 10–13). Extended time was not available to higher yield (Table 2, entry 13).



SCHEME 2: A plausible reaction mechanism.

TABLE 2: Reaction conditions in the Erlenmeyer reaction.

Entry	The amount of catalysts (mmol %)	Reaction temperature (°C)	Reaction time (h)	Isolated yields (%) <sup>a</sup>
1	0	60	4	41 <sup>b</sup>
2	2.5	60	4	67
3	5	60	4	75
4	10	60	4	76
5	20	60	4	78
6	5	25	24	15
7	5	40	4	56
8	5	60	4	75
9	5	Reflux temperature	4	62
10	5	60	1.5	53
11	5	60	2.5	56
12	5	60	4	75
13	5	60	5	75

<sup>a</sup>Based on benzaldehyde; isolated yields based on benzaldehyde; 5 mmol benzaldehyde, 5.5 mmol hippuric acid and 15 mmol acetic anhydride were used.

<sup>b</sup>Not isolated yield, some by-products were found.

To explore the scope of our catalyst, a wide variety of aldehydes were investigated in this system including aromatic and aliphatic aldehydes (Table 3, entries 1–12). Unfortunately, aliphatic aldehyde cannot be activated in this system (Table 3, entries 11–12). Interestingly, aromatic aldehydes with the electron-withdrawing groups (EWG) were present more active than that of opposite aldehydes (Table 3, entries 1–9). EDG aldehydes resulted in lower conversion and longer reaction time. Similar phenomenon was only

mentioned by Thomas's research group [1, 24, 25]. Compared to the previous report [26], it was thought that the existence of [bmim] made high catalyst activity of [bmim]<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> and [bmim]<sub>4</sub>W<sub>10</sub>O<sub>32</sub>. According to this theory and our research, it can be deduced that the existence of sulfonate may cause the different electronic effect, and a supposed reaction mechanism was given [28, 29] in Scheme 2. 2-phenyloxazol-5-one (2') was first generated in condensation reaction which happened in the presence of acetic anhydride as the dehydrating agent. The imidazolium salt could activate both aldehydic carbonyl oxygen and acidic hydrogen of 2-phenyloxazol-5-one (2'). The zwitterionic imidazolium salt (1) may act as a bifunctional organocatalyst in this reaction. The electrophilic activation of the aldehyde carbonyl is expected to take place through hydrogen bond formation with C-2 hydrogen atom of the imidazolium moiety. Similar mechanisms were indicated in the aza-Henry reaction [28] and aza-Michael addition [29].

### 3. Conclusions

In summary, imidazole-based zwitterionic-type molten salts are a new class of catalyst for the synthesis of 4-arylidene-2-phenyl-5(4H)-oxazolones through the Erlenmeyer reaction under solvent-free conditions. This present procedure is equally effective in aryl aldehydes with electron-withdrawing groups. The nonhazardous experimental conditions, ease of reaction, short reaction times, high yields, and metal-free catalyst are the notable advantages of this procedure. To the best of our knowledge, this is the first report of the Erlenmeyer reaction, promoted by a zwitterionic imidazolium salt under solvent-free conditions. The investigation of the mechanism of this reaction and the use of chiral zwitterions are underway and will be reported in due course. Thus, it provides a better and more practical alternative to the existing methodologies.

TABLE 3: Preparation of azlactones from different aldehydes.

Entry	R (aldehyde)	Reaction time (h)	Azlactones	Isolate yields (%) <sup>a</sup>	Mp found (°C)	Mp lit. (°C)
1	4-N(CH <sub>3</sub> ) <sub>2</sub>	5.5	<b>4a</b>	70	211–213	214 [25]
2	Heliotropin	5	<b>4b</b>	67	197–199	199 [30]
3	4-OCH <sub>3</sub>	5	<b>4c</b>	62	155–156	159 [25]
4	4-CH <sub>3</sub>	6	<b>4d</b>	40	143–144	144 [25]
5	H	4	<b>4e</b>	75	168–169	166 [25]
6	4-Cl	5.5	<b>4f</b>	82	196–197	196 [25]
7	2-F	4	<b>4g</b>	55	166–167	168 [31]
8	4-CF <sub>3</sub>	3	<b>4h</b>	85	173–174	174 [32]
9	4-NO <sub>2</sub>	3	<b>4i</b>	89	240–241	239 [25]
10	2-Furaldehyde	5	<b>4j</b>	35	170–172	169 [25]
11	Isobutyraldehyde	5	—	ND <sup>b</sup>	—	—
12	3-Phenylpropionaldehyde	5	—	ND <sup>b</sup>	—	—

<sup>a</sup>Based on aldehyde; isolated yields based on aldehyde; 5 mmol aldehyde, 5.5 mmol hippuric acid, 5 mmol% imidazolium salt (**1**), and 15 mmol acetic anhydride were used; the reaction was carried out at 60°C.

<sup>b</sup>No product was detected.

## 4. Experimental

**4.1. Materials.** All chemicals and solvents were obtained from commercial sources and used without further purification. Melting points were recorded on X<sub>4</sub> micro-melting apparatus and uncorrected. FT-IR spectra were recorded using KBr pellets on a Nicolet Avatar Spectrophotometer. <sup>1</sup>H NMR spectra were recorded on a Bruker Avance DMX 400 instrument using CDCl<sub>3</sub> and DMSO-d<sub>6</sub> as the solvents with TMS as an internal standard. Mass spectra were measured with an HP 5903 mass spectrometer with 70 eV energy.

**4.2. Synthesis of Imidazolium Salt (**1**) [27].** 1-methylimidazole (3.28 g, 40 mmol) was dissolved in acetone (80 mL), and 40 mL of 1,3-propanesultone (4.88 g, 40 mmol) in acetone were added slowly at 0°C. Mixtures were stirred at room temperature for 5 days in a dry N<sub>2</sub> atmosphere. The precipitate was recovered and washed by filtration and dried *in vacuo* at 60°C. White solid; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ = 2.09 (t, 2H, J = 7.0 Hz, CH<sub>2</sub>), 2.45 (t, 2H, J = 11.3 Hz, CH<sub>2</sub>), 3.85 (s, 3H, CH<sub>3</sub>), 4.31 (d, 2H, J = 6.8 Hz, CH<sub>2</sub>), 7.69 (s, 1H), 7.78 (s, 1H), 9.11 (s, 1H).

**4.3. Synthesis of 4-Phenyl-4-(phenylmethylene)-5(4H)-oxazolone (**4e**).** A mixture of benzaldehyde (505 μL, 5 mmol), hippuric acid (0.98 g, 5.5 mmol), acetic anhydride (1.6 mL, 15 mmol), and imidazolium salt (0.051 g, 0.25 mmol) was taken in a dry 50 mL flask with constant stirring. The whole mixture was stirred at 60°C in oil bath for appropriate time (by TLC). The filtrate was cooled to room temperature, 5 mL 95% EtOH were added, and yellow solid was precipitated. The yellow solid was filtered off and washed with hot water. The crude azlactone was purified by recrystallisation from acetone/water (0.934 g, 75% as yellow solid). M.p. 168–169°C (Lit. [25] M.p. 168°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.27 (s, 1H, -CH=), 7.48–7.63 (m, 6H, ArH), 8.19–8.23 (m, 4H, ArH). IR (KBr) 3420, 1793 (-C=O), 1653, 1384, 1167 cm<sup>-1</sup>.

Mass (*m/z*): 249, 116, 105, 89. See Supplementary Material available at <http://dx.doi.org/10.1155/2013/280585>.

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## Research Article

# Cycloaddition Reaction of Carbon Dioxide to Epoxides Catalyzed by Polymer-Supported Quaternary Phosphonium Salts

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Polymer-supported quaternary phosphonium salt (PS-QPS) was explored as effective catalyst for the coupling reaction of carbon dioxide with epoxides. The results indicated that cyclic carbonates with high yields (98.6%) and excellent selectivity (100%) could be prepared at the conditions of 5 MPa CO<sub>2</sub>, 150°C, and 6 h without the addition of organic solvents or cocatalysts. The effects of various reaction conditions on the catalytic performance were investigated in detail. The catalyst is applicable to a variety of epoxides, producing the corresponding cyclic carbonates in good yields. Furthermore, the catalyst could be recovered easily and reused for five times without loss of catalytic activity obviously. A proposed mechanism for synthesis of cyclic carbonate in the presence of PS-QPS was discussed. The catalyst was characterized by thermogravimetric analysis (TGA), scanning electron microscopy (SEM), and Fourier transform infrared (FT-IR) spectrum. It is believed that PS-QPS is of great potential for CO<sub>2</sub> fixation applications due to its unusual advantages, such as easy preparation, high activity and selectivity, stability, low cost, and reusability.

## 1. Introduction

Due to the economic and environmental benefits, developing chemical synthesis processes using renewable resource becomes increasingly important [1]. From the green chemistry point of view, the use of CO<sub>2</sub> as feedstock in synthesis and industrial applications plays an important role in the protection of environment because it is a primary greenhouse gas which contributes to global warming, and the emission of CO<sub>2</sub> from combustion into the atmosphere continues to rise [2, 3]. Without action toward stemming CO<sub>2</sub> emissions, global warming could pose a massive threat to our modern life; crop failure due to changing climates, increasingly common freak weather conditions, and loss of habitat are all potential consequences of humans carbon-rich lifestyle which are already becoming apparent [4, 5].

Carbon dioxide is an attractive C1 building block, safe raw material, and environmentally friendly chemical reagent in organic synthesis since it is highly abundant, inexpensive, nontoxic, and nonflammable [6, 7]. Therefore, chemical fixation of CO<sub>2</sub> becomes more important from both an ecological and an economic points of view. Approximately

110 MT (megatons) of CO<sub>2</sub> are currently used for chemical synthesis annually. The chemicals synthesized include urea, salicylic acid, cyclic carbonates, and polycarbonates [8]. The cycloaddition reaction of CO<sub>2</sub> with epoxides to afford the five-membered cyclic carbonates represents a promising methodology in CO<sub>2</sub> chemical fixation [9, 10], these cyclic carbonates can be widely used for various purposes, such as electrolytic elements of lithium secondary batteries, polar aprotic solvents, monomers for synthesizing polycarbonates, chemical ingredients for preparing medicines or agricultural chemicals, alkylating agents, engineering plastics, and biomedical fields [11, 12]. In the last decades, many catalytic systems have been developed for coupling CO<sub>2</sub> and epoxides, such as metal salts [13], metal oxides [14], quaternary ammonium salts [15, 16], quaternary phosphonium salts [17, 18], transition metal complex, salen complex [19–25], ion-exchange resins [26], and ionic liquids (ILs) [27–31]. However, in some of the cases, organic solvents and expensive metal catalysts are used in the reactions or work-up procedures, and the products are commonly isolated from the reaction systems by distillation; the yield of the desired products still remained low. Therefore, development

TABLE 1: Cycloaddition reactions of CO<sub>2</sub> to ECH catalyzed by different catalysts.

Catalyst	P content (%)	Yield (%)	Selectivity (%)
PS-QPS-1	5.0	98.6	99.4
PS-QPS-2	2.1	78.9	97.9
PIL-1	8.7	93.3	100
PIL-2	9.4	92.4	97.4
PBu <sub>3</sub>	15.3	5.3	89.6
CMPS	0	—	—

Reaction conditions: ECH 3 mL, catalyst 0.08 g, 5 MPa CO<sub>2</sub>, 150 °C, and 6 h.

of efficient catalysts for this transformation using cheap and nontoxic reagents and conducting the reactions under solvent-free conditions are still desirable [32].

In the previous works [33–35], we found that quaternary phosphonium salts demonstrated very high activity and excellent selectivity in the cycloaddition of CO<sub>2</sub> to epoxides. Herein, we highlight the use of high cross-linked polymeric material as support and develop the polymer-supported quaternary phosphonium salts (PS-QPS) for the synthesis of cyclic carbonate (as shown in Scheme 1). The catalytic performance of PS-QPS catalyst for cycloaddition of CO<sub>2</sub> to epoxides was investigated in detail.

## 2. Experimental

**2.1. Materials.** Highly cross-linked chloromethylated polystyrene (CMPS) (substitution: 4.7 mmol/g and 2% cross-linked with divinylbenzene, particle size: 100–200 mesh) was purchased from Tianjin Nankai Hecheng Sci. & Tech. Co. Ltd. Epichlorohydrin (ECH, AR) and propylene oxide (PO, CP) were commercially available and distilled before use. Tributylphosphine (PBu<sub>3</sub>), cyclohexene oxide (Aladdin), styrene oxide (Aladdin 98%), allyl glycidyl ether (AGE, Aladdin > 99.0%) and carbon dioxide (99.99%), were used without further purification. Other chemicals were commercially available and used as received.

**2.2. Synthesis of 4-Vinylbenzyl-Tributylphosphorous Chloride (PIL-1).** 4-Vinylbenzyl-tributylphosphorous chloride was synthesized according to the reported method [33–35]. 4-Vinylbenzyl chloride (4.03 g, 26.4 mmol), PBu<sub>3</sub> (5.36 g, 26.5 mmol), and acetone (50 mL) were introduced into a dried flask with a magnetic stirrer. The mixture was stirred at 60 °C under nitrogen for 48 h. Then, 4-vinylbenzyl-tributylphosphorous chloride (PIL-1) was obtained by filtration after pouring the mixture into diethyl ether and washed with diethyl ether. The solid was dried overnight under vacuum at room temperature to give a white powder (yield: 78.6%). 4-Vinylbenzyl-tributylphosphorous chloride was characterized by proton nuclear magnetic resonance (<sup>1</sup>H NMR, D<sub>2</sub>O, 400 MHz, δ ppm): 0.68 (*t*, 9H), 1.12–1.36 (*m*, 6H), 1.88 (*s*, 6H), 3.39 (*t*, 6H), 5.11 (*d*, 2H), 5.65 (*d*, 1H), 6.45–6.63 (*m*, 2H), and 7.0–7.4 (*m*, 4H). Benzyl-tributylphosphorous chloride (PIL-2) was synthesized according to the same procedure (yield: 80.0%)—<sup>1</sup>H NMR

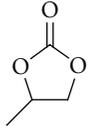
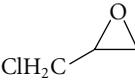
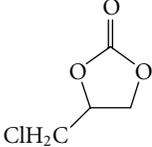
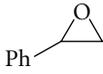
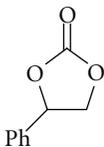
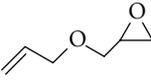
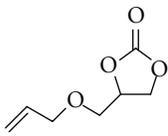
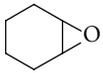
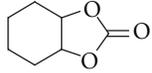
(D<sub>2</sub>O, 400 MHz, δ ppm): 0.94 (*t*, 9H), 1.38–1.52 (*m*, 6H), 1.52–1.67 (*m*, 6H), 2.05–2.08 (*m*, 6H), 3.65–3.79 (*d*, 2H), and 7.31–7.58 (*m*, 5).

**2.3. Preparation of Polymer-Supported Quaternary Phosphonium Salts.** Preparation of immobilized quaternary phosphonium salts on chloromethylated polystyrene (CMPS) was conducted according to the procedure in the literature with a little modification [36]. A mixture of CMPS (0.38 g, 1.8 mmol), tributylphosphine (2.1 mmol), and acetonitrile (60 mL) was refluxed for 48 h under a nitrogen atmosphere in a 100 mL flask. After cooled down to room temperature, the solid residue was collected by filtration and washed three times with dehydrated ethanol. Then, the solid was dried under vacuum at 60 °C for 12 h to give polymer-supported quaternary phosphonium salt (PS-QPS).

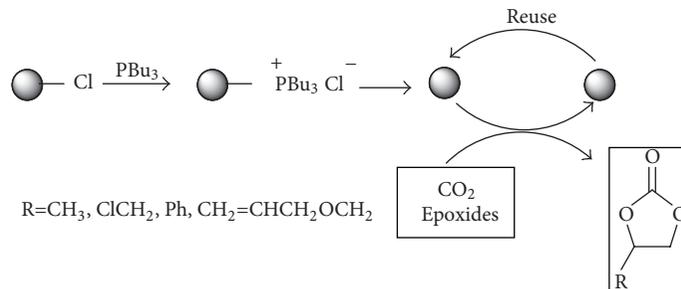
**2.4. Characterization of Polymer-Supported Quaternary Phosphonium Salts.** Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on a Bruker AM 400 MHz spectrometer at 25 °C. Thermogravimetric analysis (TGA) was performed using a TG-DTA 2000S (Mac Sciences Co. Ltd., Yokohama, Japan) in a nitrogen atmosphere between 25 and 800 °C at a heating rate of 10 °C/min. Fourier transform infrared (FT-IR) spectra were recorded on a DigiLab FTS-3000 IR-spectrometer with anhydrous potassium bromide (KBr) as standard. The morphology of PS-QPS was observed by scanning electron microscope (JSM 6701F, Japan). The content of P element was determined by atom absorbance spectrograph using a PerkinElmer optima 4300 DV as emission spectrometer (USA).

**2.5. Typical Procedure for the Synthesis of Cyclic Carbonate from ECH and CO<sub>2</sub>.** The cycloaddition reactions were performed in a 100 mL stainless steel autoclave equipped with a magnetic stirrer. For each typical batch operation, epoxides and PS-QPS were charged into the reactor and then purged with CO<sub>2</sub>. The reactor was then pressurized with CO<sub>2</sub> to a preset pressure at room temperature. The reactor was heated to a specified temperature with an addition of CO<sub>2</sub> from a high-pressure reservoir tank to maintain a specified constant pressure for a desired time, and then the reaction was started by stirring the reactant mixture at 300 rpm. The reactor pressure increased about 0.03–0.10 MPa depending on the reaction temperature due to vapor pressure of the reactants. After the proper reaction time, the reactor was cooled to 0–5 °C in an ice-water bath, and then the CO<sub>2</sub> was released through a cold trap with *N,N*-dimethylformamide to capture the reactants and products entrained by CO<sub>2</sub>. The organic products were filtrated from the reaction mixture and the resulting filtrate, together with the absorbent, was analyzed by gas chromatography (GC, GC-16 A, 3 m · 3 mm OV-17 column, Shimadzu). The retention time of the products was compared with available authentic standards. The synthesized catalysts were pretreated by grinding before use.

TABLE 2: Cycloaddition reactions of CO<sub>2</sub> to different epoxides.

Entry	Epoxides	Products	Time (h)	Selectivity (%)	Yield (%)
1			6	99.9	93.0
2			6	99.4	98.6
3			10	98.6	95.8
4			9	79.2	73.7
5			48	88.2	72.3

Reaction conditions: epoxide 3 mL, PS-QPS-1 0.08 g, 5 MPa CO<sub>2</sub>, 150 °C.

SCHEME 1: Preparation of PS-QPS and cycloaddition reaction of CO<sub>2</sub> to epoxides.

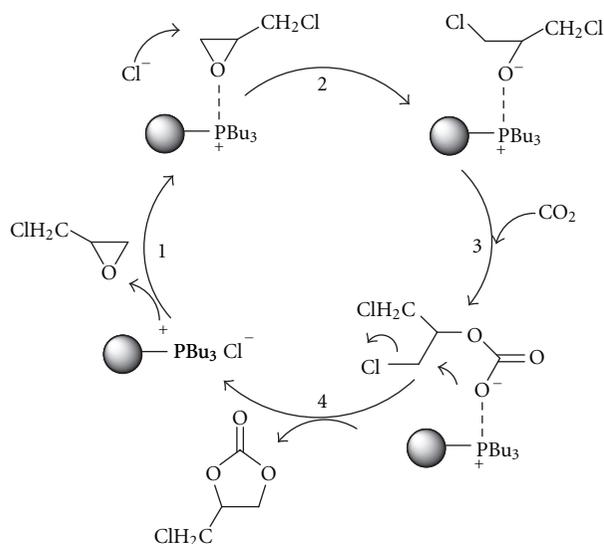
### 3. Results and Discussion

**3.1. Characterization of Catalyst.** Figure 1 shows the FT-IR spectra of CMPS, as well as fresh and used PS-QPS. The peaks at 1459 and 703 cm<sup>-1</sup>, ascribing to the stretching vibration of P-C(Ar) and P-C, respectively, emerged in PS-QPS curve. In addition, there is a wide and strong peak at 3430 cm<sup>-1</sup>, which is ascribed to absorption of H-O in water molecular. It is because PS-QPS becomes hydrophilic due to the introduction of quaternary phosphonium salts on the surface. However, the surface of CMPS is hydrophobic. The previous results indicate that tributylphosphine has been anchored onto CMPS successfully.

Figure 2 gives the TGA curves of PS-QPS and CMPS. It is observed that the weight loss of CMPS is less than 1% up to 260 °C. And then, polymer matrix decomposition goes

through two stages, at 270 °C and 430 °C, respectively. However, there is about 8% weight loss in PS-QPS below 110 °C. This may be attributed to the desorption of trapped water on the surface of PS-QPS. Polymer matrix decomposition of PS-QPS begins at 290 °C and higher than CMPS (270 °C). It can be drawn that the thermal stability of CMPS was enhanced a little due to the graft of tributylphosphine. Moreover, there is only 20% weight loss at 380 °C in CMPS, whereas the weight loss of PS-QPS is as high as 50% at the same temperature. It can be inferred that more weight loss is ascribed to the decomposition of tributylphosphine on the surface of PS-QPS.

As discussed earlier, the surface of PS-QPS became hydrophilic due to the anchoring of tributylphosphine. It can also be proved by SEM images. As shown in Figure 3, the surface of CMPS with the size about 100 μm is quite plain



SCHEME 2: Proposed mechanism for PS-QPS catalyzed cycloaddition of  $\text{CO}_2$  with epoxides.

(Figures 3(a) and 3(d)). When CMPS was modified with quaternary phosphonium salts and recycled in the cycloaddition reaction, the size of CMPS particles did not change. However, it can be seen clearly that many spherical particles in the size of about 200 nm can be observed (Figure 3(e)). It is because quaternary phosphonium salt is hydrophilic, whereas CMPS is hydrophobic. As a result, phase separation occurs, and quaternary phosphonium salts tend to aggregate together to form spherical particles.

**3.2. Coupling Carbon Dioxide and Epichlorohydrin.** The catalytic performances of PS-QPS catalysts with different phosphorus content for the cycloaddition reaction of  $\text{CO}_2$  to epichlorohydrin (ECH) were investigated. The phosphorus contents of different PS-QPS were determined by atom absorbance spectrograph. The results are summarized in Table 1. It can be seen that CMPS does not exhibit any activity for the cycloaddition reaction. However, PS-QPS presents high activity and selectivity at the same conditions, and the yield of cyclic carbonate increases with  $P$  content of PS-QPS microparticles. The catalytic activity of PS-QPS-1 is even higher than the unsupported quaternary phosphorous salts (PIL-1 and PIL-2). The main reason for this was that ionic liquids catalysts were immiscible with the substrate, and there were two phases in the reaction system at the beginning [36]. As a result, the interphase mass transfer reduced the reaction rate, while PS-QPS microparticles synthesized in this work could be well dispersed in the reaction mixture under stirring.

**3.3. Influences of Pressure and Temperature on the Synthesis of Cyclic Carbonate.** A disadvantage associated with using  $\text{CO}_2$  as a reagent in organic synthesis is the potential dangers resulted from operating at high temperatures and pressures, especially in the presence of heterogeneous catalytic system. Therefore, the independences of the yields of cyclic carbonate on the reaction conditions were investigated. Figure 4 depicts

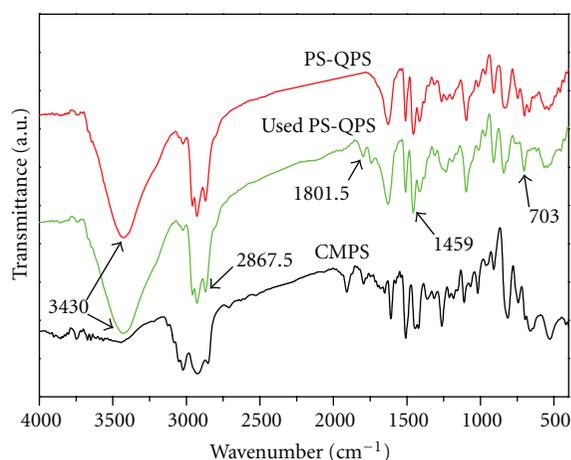


FIGURE 1: FT-IR spectra of chloromethylated bead and PS-QPS.

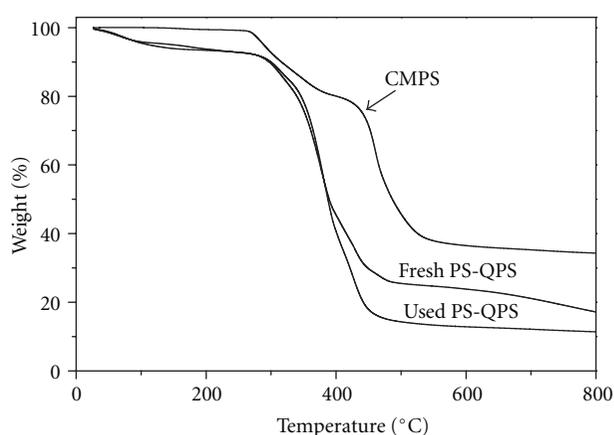


FIGURE 2: TGA curves of PS-QPS and chloromethylated bead.

the effect of  $\text{CO}_2$  pressure on the yield of cyclic carbonate in the presence of PS-QPS. It can be seen that pressure plays great influence on the yield of cyclic carbonate. A yield of 77.5% can be obtained at lower pressure (2 MPa), and it increases with the  $\text{CO}_2$  pressure from 2 to 5 MPa. The cyclic carbonate yield achieves as high as 98% when the reaction is conducted at 5.0 MPa  $\text{CO}_2$ . However, the yield decreases to 91.6% when further increasing the pressure up to 5.5 MPa. This can be explained by the pressure effect on the concentrations of  $\text{CO}_2$  and epoxide in the two phases [37]. The upper phase is the  $\text{CO}_2$ -rich phase, and the bottom phase is the epoxide-rich phase. The reactions take place mainly in the liquid phase because the catalyst is dispersed in this phase. The change in reaction rate is related to the partition behavior of the substrate, and the increase in  $\text{CO}_2$  pressure has two opposite effects on the reactions. First, the solubility of  $\text{CO}_2$  in the epoxides increases with increasing pressure, which favors the reaction considering that  $\text{CO}_2$  is a reactant. At higher pressures, however, more epoxides are in the  $\text{CO}_2$ -rich phase and the concentration of epoxides in the liquid phase is too low, which reduces the reaction rate. At lower  $\text{CO}_2$  pressure, the first factor is dominant because

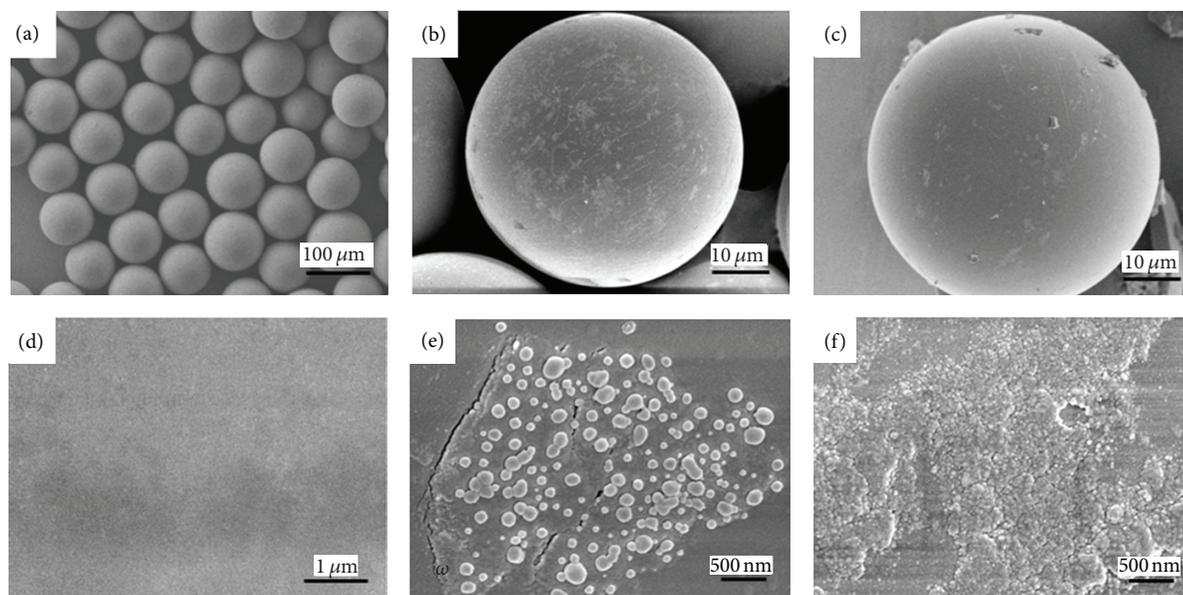


FIGURE 3: SEM images of chloromethylated bead (a and d), fresh PS-QPS (b and e), and used PS-QPS (c and f).

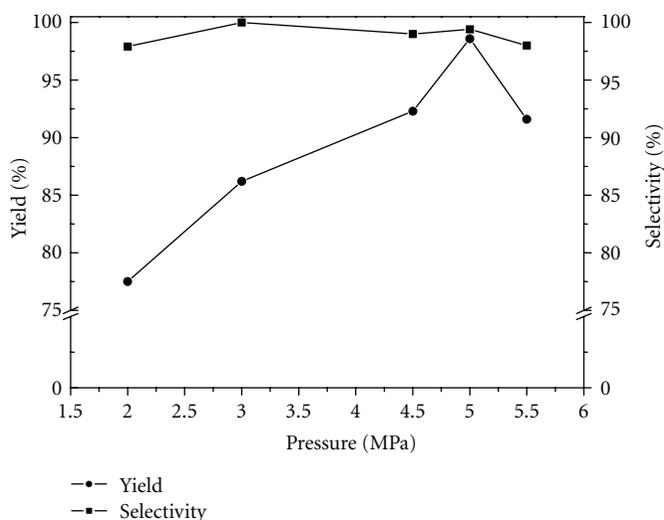


FIGURE 4: Dependence of the cyclic carbonate yield and selectivity on CO<sub>2</sub> pressure. Reaction conditions: ECH 3 mL, PS-QPS-1 0.08 g, 150°C, and 6 h.

the concentration of CO<sub>2</sub> in the liquid phase is lower. The second factor becomes dominant when the pressure of CO<sub>2</sub> is high enough. Therefore, a maximum appears in pressure versus yield curve [38]. The maximum occurs in yield versus pressure curves at about 5 MPa for ECH in the present system.

Figure 5 shows the influence of temperature on the yield and selectivity of cyclic carbonate. It can be seen clearly that the catalytic activity is sensitive to reaction temperature. The yield of cyclic carbonate increases dramatically with the temperature increasing from 130°C to 150°C. However, the yield decreases when further increasing the temperature. It has been reported that there were some side reactions, such as ECH polymerization, the isomerization to acetone

and the ring opening by water to propylene glycol [29, 39]. The GC study showed that the by-product in the present cycloaddition reaction of ECH was 3-chloro-1,2-propylene glycol. Therefore, the main side reaction was the ring opening of cyclic carbonate caused by the residual water on the surface of PS-QPS microparticles at higher temperature.

**3.4. Influences of Reaction Time and Catalyst Amount on the Synthesis of Cyclic Carbonate.** Dependence of the product yield on reaction time at 150°C and CO<sub>2</sub> pressure of 5 MPa is shown in Figure 6. It indicates that the yield increased with reaction time, and 98.6% ECH can be converted within 6 h. In other words, PS-QPS is an effective heterogeneous catalyst

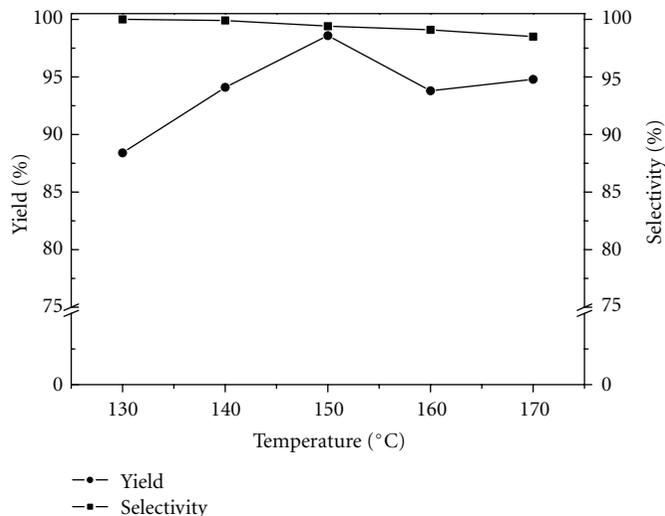


FIGURE 5: Temperature dependence of the cyclic carbonate yield and selectivity. Reaction conditions: ECH 3 mL, PS-QPS-1 0.08 g, 5 MPa CO<sub>2</sub>, 6 h.

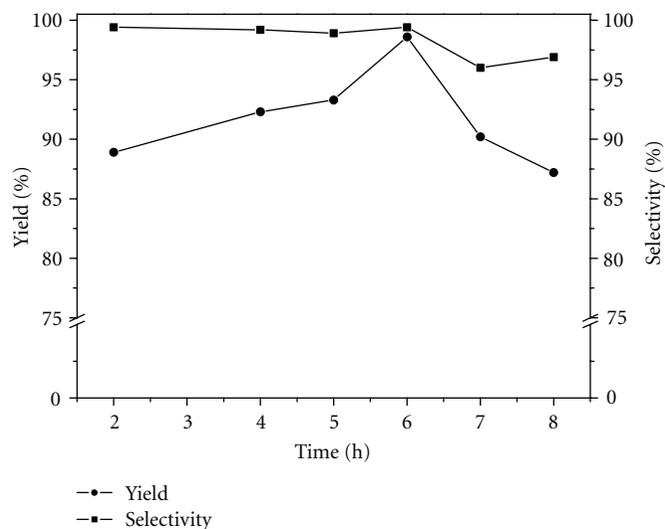


FIGURE 6: Influence of reaction time on the cyclic carbonate yield and selectivity. Reaction conditions: ECH 3 mL, PS-QPS-1 0.08 g, 5 MPa CO<sub>2</sub>, and 150°C.

for the synthesis of cyclic carbonate from ECH and CO<sub>2</sub>. However, both the yield and selectivity undergo decreases with the reaction time increasing, especially the yield. It has been reported that supported ionic liquid was also active catalyst for the hydrolysis reaction of cyclic carbonate to produce 1,2-propylene glycol [40]. As shown in Figures 2 and 3, the microparticles surface became highly hydrophilic, and some water was absorbed after quaternary phosphorous salts were anchored onto. Therefore, the reason for the decrease of cyclic carbonate yield with the reaction time over 6 hours is presumably due to the hydrolysis of cyclic carbonate to 3-chloro-1,2-propylene glycol. Similarly, GC results testified

the previous conclusion. Thus, all the following reactions are performed in 6 h.

The influence of catalyst amount on the reaction was also evaluated under otherwise identical reaction conditions. As summarized in Figure 7, the yield of cyclic carbonate remarkably increases to 87.9% with 0.07 g catalyst presented. Notably, cyclic carbonate could be obtained in almost quantitative yield (98.6%) with 99.4% selectivity within 6 h when the catalyst amount increased to 0.08 g. A lower cyclic carbonate yield was observed when the catalyst amount increased further. Because the catalyst microparticles are highly charged, there is electrostatic interaction between

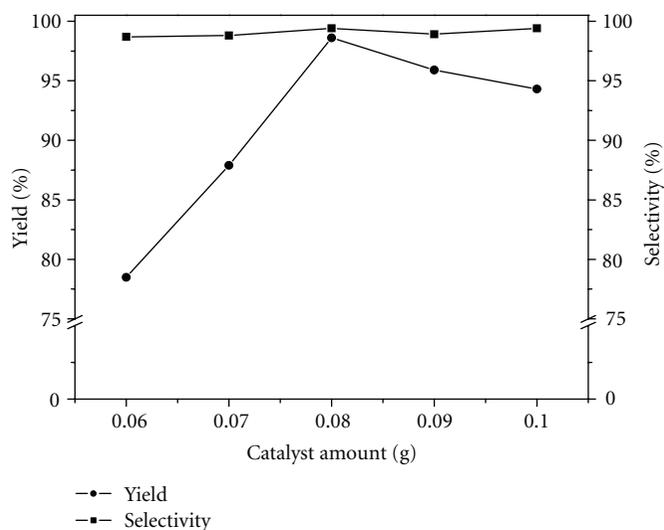


FIGURE 7: Effect of the amount of catalyst on the cyclic carbonate synthesis. Reaction conditions: ECH 3 mL, PS-QPS-1, 5 MPa CO<sub>2</sub>, 150°C, and 6 h.

these catalyst microparticles. Therefore, the excess catalysts cannot be well dispersed in the reaction mixture and limit the mass transfer between the active sites and reactants [30]. As a result, there is an optimal catalyst amount in the present cycloaddition reaction process.

**3.5. Coupling Carbon Dioxide and Other Epoxides.** The results previous indicated that PS-QPS is an effective catalyst for the cycloaddition of ECH with CO<sub>2</sub> at solvent-free and cocatalyst-free conditions. In order to survey the scope of substrates, we examined the cycloaddition reactions of CO<sub>2</sub> with other epoxides by performing the reaction under the same conditions as elaborated in Table 2. PS-QPS is found to be applicable to a variety of terminal epoxides (entries 1–5, Table 2) to provide the corresponding cyclic carbonates with high yields and selectivity. Entries 1 and 2 demonstrate that ECH is more reactive than propylene epoxide when PS-QPS was used as catalyst. The possible reason is the presence of the electron-withdrawing chloromethyl group in ECH, which results in easy ring opening of ECH by nucleophilic attack. Due to the higher hindrance originated from the two rings, cyclohexene oxide (entry 5) presents relatively lower activity [11].

A possible mechanism for the PS-QPS-catalyzed cycloaddition of CO<sub>2</sub> with epoxide is proposed as shown in Scheme 2. As mentioned earlier, the quaternary phosphonium salt part is suggested to be the active species for the reaction. This proposal is analogous to that of the quaternary phosphonium salt-catalyzed version of the same reaction [5]. The proposed mechanism involves the activation of epoxide by the quaternary phosphonium cation (step 1), the ring opening of the epoxides via nucleophilic attack of chlorine at the less-hindered carbon, producing an oxy anion species (step 2), and the insertion of CO<sub>2</sub> into the P–O bond (step 3). Subsequent cyclization via an intermolecular nucleophilic attack (step 4) leads to the cyclic carbonate and

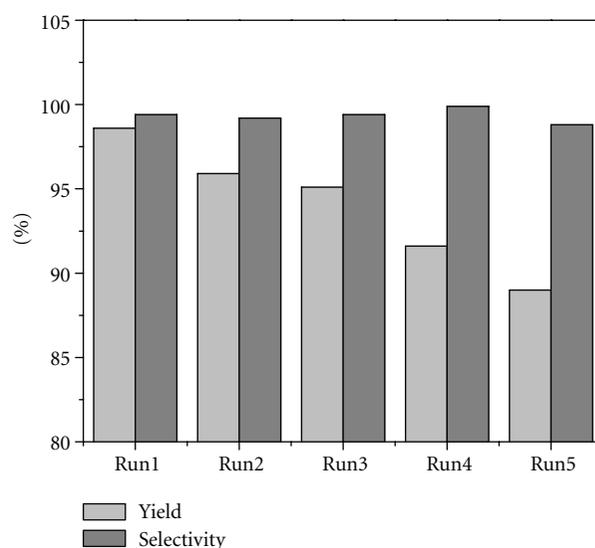


FIGURE 8: Recycling experiments for polymer-supported quaternary phosphonium salts. Reaction conditions: ECH 3 mL, PS-QPS-1 0.08 g, 5 MPa CO<sub>2</sub>, 150°C, and 6 h.

the regeneration of the catalyst. It can be seen that the role of resin in this system was as a reusable supporter which can be easily separated.

It is well known that the constancy of the catalyst activity and reusability of catalyst are two important factors that determine whether it finds practical application in industry. In order to test this characteristic of PS-QPS catalyst, a series of catalytic cycles for the coupling reaction of CO<sub>2</sub> with ECH are investigated under the optimized reaction conditions [21, 29]. In each cycle, the catalyst was separated by filtration, washed with acetone, and then dried under vacuum before use in the succeeding run. The yields of cyclic carbonates after five repeated runs are shown in Figure 8. There is only about

10% activity loss after five recycles, indicating that the catalyst is not only insoluble in the reaction mixture but also very stable. The loss of catalytic activity may be due to the residual cyclic carbonate in PS-QPS. It is very difficult to remove cyclic carbonate from the catalyst completely due to its high boiling point (above 200°C). The residual cyclic carbonate in the catalyst can be testified by FT-IR. As shown in Figure 1, the peak at 1801.5 cm<sup>-1</sup> in the curve of used PS-QPS is ascribed to the stretch vibration of C=O in cyclic carbonate. Moreover, SEM image (Figure 3(f)) indicates that spheric particles on the surface of PS-QPS disappear, and the surface of used PS-QPS becomes rougher. It may be due to the solubilization of cyclic carbonate. TGA curve (Figure 2) illustrates that used PS-QPS is thermally stable.

#### 4. Conclusions

Tributylphosphine was anchored on highly cross-linked chloromethylated polystyrene as effective catalyst for cyclic carbonates synthesis via the cycloaddition of epoxides with CO<sub>2</sub>. The results testified that high yields and excellent selectivity can be achieved using PS-QPS on the condition of 5 MPa CO<sub>2</sub> and 150°C in 6 h. In addition, the catalyst can be easily separated from the products and reused for up to five times without considerable decrease in the yield of cyclic carbonate. The organic solvent-free green process presented here is of great potential application in industry due to its easy product separation, low cost, and high efficiency. In the future work, we will explore the application of PS-QPS catalyst in the transesterification reaction of cyclic carbonate and methanol for dimethyl carbonate synthesis. And our aim is the industry application of these quaternary phosphonium salt-based heterogeneous catalysts.

#### Acknowledgments

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## Research Article

# Ionic-Liquid-Mediated MacMillan's Catalyst for Diels-Alder Reaction

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Ionic liquids were used to enhance as well as recycle the MacMillan's catalyst **1** for the Diels-Alder reaction. Using our developed protocol, Diels-Alder adducts were obtained in good yields and selectivities along the 6 times recycling of MacMillan's imidazolidinone catalyst **1**. Synthesis of steroid **4** is the major outcome of our developed protocol.

## 1. Introduction

Over the past decade, the Diels-Alder reaction is found highly applicable as the most powerful organic reaction in area of chemical synthesis [1–5]. In recent times much interest has been developed for the synthesis of highly efficient organocatalysts for a variety of organic transformations [6–10]. MacMillan and coworkers have initially reported (5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride catalyst (MacMillan's imidazolidinone catalyst **1**), as a promising organocatalyst for the Diels-Alder reaction *via* a LUMO-lowering activation reaction mechanism [8, 11, 12]. Although the MacMillan's imidazolidinone catalyst **1** was found highly active in terms of yield and selectivity but still this catalyst has suffered from various drawbacks like the need for high catalyst loading, requirement of polar solvents, catalyst recycling, and so forth [13–17]. To avoid such drawbacks and to make the MacMillan's imidazolidinone catalyst **1** more convenient for Diels-Alder reaction, various approaches have been reported from different groups to support this MacMillan's imidazolidinone catalyst **1** *via* ionic liquids [13], polymethylhydrosiloxane polymer [14], Montmorillonite [15], and so forth. The supported organocatalysts seem particularly attractive because they offer homogeneous/heterogeneous reactions medium, high selectivity, low catalyst loading, catalyst recycling, and so forth, but this supported system also carries various demerits

like requirement of costly starting materials, long preparation steps (3–4 steps), tedious work-up procedures, and lack of catalyst recycling.

In various reports, ionic liquids were also identified as an alternative solvent to immobilize not only to MacMillan's imidazolidinone catalyst **1** for the Diels Alder reaction [16, 17] but some organocatalysts too for various useful organic transformations. Recycling of catalytic, low catalyst loading and option to avoid the use of polar solvents are the major outcomes of ionic-liquid-mediated catalysis [17]. Considering the above facts and merits of ionic liquid immobilized organocatalysis, we initiated our work in the area of ionic liquid immobilized MacMillan's imidazolidinone catalyst **1** for Diels-Alder reaction.

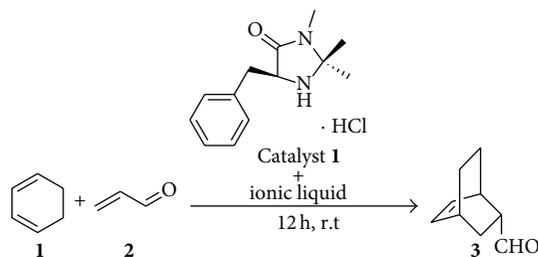
## 2. Experimental Procedure

All the chemicals were purchased from Sigma Aldrich, Acros, or SD fine chemicals, and all the experiments were carried out under nitrogen unless noted. NMR spectra were recorded on standard Bruker300WB spectrometer with an Avance console at 300 and 75 MHz for <sup>1</sup>H and <sup>13</sup>C NMR, respectively. Enantiomeric excesses were determined by chiral-phase HPLC: Waters 600E System Controller and Waters 996 Photodiode Array Detector Column with Chiralcel AS-H, Chiralcel OD-H, and Chiralcel AD-H column from Daicel

TABLE 1: Screening of different ionic liquids for MacMillan's imidazolidinone catalyst **1** catalysed Diels-Alder reaction between cyclohexene **1** and acrolein **2**.

Entry	Ionic liquid	Ionic liquid amount (in mmol)	Yield <sup>a</sup> (%)	<i>endo</i> : <i>exo</i> <sup>b</sup>	ee (%) <sup>c</sup>
(1)	[bmim][Cl]	0.05	64	1.5 : 1	65
		0.10	63	1.6 : 1	67
(2)	[bmim][PF <sub>6</sub> ]	0.05	68	1.8 : 1	71
		0.10	70	2.2 : 1	74
(3)	[bmim][NTf <sub>2</sub> ]	0.01	65	3 : 1	71
		0.02	68	3.5 : 1	78
		0.05	84	4.2 : 1	88
		0.10	91	5.6 : 1	92
		0.5	94	19 : 1	95
		1	92	96 : 1	91
(4)	MeOH/H <sub>2</sub> O	0.95 mL : 0.05 mL	8	2.3 : 1	87
(5)	CH <sub>3</sub> CN/H <sub>2</sub> O	0.95 mL : 0.05 mL	84	2.3 : 1	90

<sup>a</sup>Isolated yield, <sup>b</sup>*endo*:*exo* ratio was determined by <sup>1</sup>H NMR, <sup>c</sup>ee% was determined by HPLC, <sup>d</sup>1 mL MeOH/H<sub>2</sub>O system.



SCHEME 1: Ionic-liquid-mediated Diels-Alder reaction.

Chemical Industries Ltd., eluting with *n*-hexane and 2-propanol.

**2.1. General Methods for Ionic Liquid Mediated Diels-Alder Reaction.** Ionic liquid (0.5 mmol) or MeOH (0.95 mL)/Water (0.05 mL) or CH<sub>3</sub>CN (0.95 mL)/water (0.05 mL), MacMillan's imidazolidinone catalyst **1** (0.02 mmol), cyclohexadiene **1** (0.5 mmol), acrolein **2** (2.5 mmol), and CF<sub>3</sub>COOH (5 mol%) were allowed to stir for 12 h at room temperature. The corresponding reaction product from the well-dried reaction mass (dried under high vacuum at 50 °C for 1 hour in order to remove all volatile impurities) was extracted with ether (5 × 2 mL). Combined organic layers were dried over high vacuum, and the reaction mixture was further purified by column chromatography.

**2.2. Recycling of the Catalytic System.** The recycling experiments were carried out using [bmim][NTf<sub>2</sub>] (0.5 mmol) and MacMillan's imidazolidinone catalyst **1** (0.02 mmol) for the model Diels-Alder reaction between cyclohexadiene **1** (0.5 mmol), acrolein **2** (2.5 mmol), and CF<sub>3</sub>COOH (5 mol%) at RT for 12 h. After completion of the first run, the reaction product was isolated with simple ether washing. The remaining reaction mass was allowed to dry under high vacuum at 50 °C for 1 hour in order to remove all the volatile impurities

from the reaction mass and then the reaction mass (mixture of [bmim][NTf<sub>2</sub>]/(5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride) subjected to Diels-Alder reaction.

**2.3. Synthesis of Steroid 4.** Ionic liquid (0.5 mmol), MacMillan's imidazolidinone catalyst **1** (0.02 mmol), 7-methoxy-4-vinyl-1,2-dihydronaphthalene **1** (0.5 mmol), 2-Bromo-propenal **2** (2.5 mmol), and CF<sub>3</sub>COOH (5 mol%) were allowed to stir for 12 h at room temperature. The corresponding reaction product from the well-dried reaction mass (dried under high vacuum at 50 °C for 1 hour in order to remove all the volatile impurities) was extracted with hexane:ethylacetate (20% mixture) (5 × 2 mL). Combined organic layers were dried over high vacuum, and the reaction mixture was further purified by column chromatography.

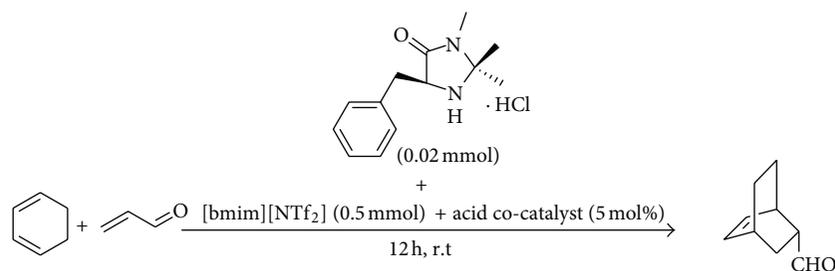
### 3. Result and Discussion

As reported in Table 1, three different types of ionic liquid like [bmim][Cl], [bmim][PF<sub>6</sub>], and [bmim][NTf<sub>2</sub>] were tested as a reaction medium for MacMillan's imidazolidinone catalyst **1** to catalyzed our model Diels-Alder reaction between cyclohexadiene **1** and acrolein **2** (Scheme 1 and Table 1, Entry 1–3). As shown in Table 1 at room temperature our

TABLE 2: Screening of Acid cocatalysts for [bmim][NTf<sub>2</sub>] mediated Diels-Alder reaction with MacMillan's imidazolidinone catalyst **1**.

Entry	Acid co-catalyst	Yield <sup>a</sup> (%)	<i>endo</i> : <i>exo</i> <sup>b</sup>	ee <sup>c</sup> (%)
(1)	CF <sub>3</sub> COOH	98	19:1	97
(2)	CH <sub>3</sub> COOH	90	19:1	95
(3)	TfOH	95	18:1	94
(4)	<i>p</i> -TSA	96	18:1	92
(5)	Cl <sub>3</sub> COOH	20	17:1	87
(6)	HCl	75	17:1	92
(7)	Ph-COOH	76	17:1	89

<sup>a</sup>Isolated yield, <sup>b</sup>*endo*:*exo* ratio was determined by <sup>1</sup>HNMR, <sup>c</sup>ee% was determined by HPLC.

SCHEME 2: [bmim][NTf<sub>2</sub>] mediated Diels-Alder reaction with MacMillan's imidazolidinone catalyst **1**.

model Diels-Alder reaction enjoyed a lot with [bmim][NTf<sub>2</sub>] (0.5 mmol) mediated catalyst **1** and offered the desired product **3** with high yield (82% yield) and selectivity (24:1 *endo*:*exo*, 94% ee). Comparatively, lower yields and selectivities were obtained for the same model reaction (Table 1, Entry 1, 2) with both [bmim][Cl] and [bmim][PF<sub>6</sub>], as the MacMillan's imidazolidinone catalyst **1** was almost insoluble in both [bmim][Cl] and [bmim][PF<sub>6</sub>]. Instead of ionic liquids, MacMillan's imidazolidinone catalyst **1** was also treated with MeOH/H<sub>2</sub>O solvent system for same model Diels-Alder reaction. The corresponding product **3** was obtained in an acceptable yield (68%) along with 2.3:1 *endo*:*exo* ratio and 72% ee.

Various acids were also tested to improve the yield and selectivity of Diels-Alder reaction (Table 2 and Scheme 2). The utilization of CF<sub>3</sub>COOH, TfOH, CH<sub>3</sub>COOH and *p*-TSA led to relatively good yields and selectivity for [bmim][NTf<sub>2</sub>] mediated Diels-Alder reaction with MacMillan's imidazolidinone catalyst **1**. In contrast, relatively high yield (98%) and excellent enantioselectivity (97%) with good *endo*:*exo* ratio were obtained (>19:1) and produced when CF<sub>3</sub>COOH, was selected. Thus, CF<sub>3</sub>COOH was identified as the optimal acidic cocatalyst.

Having the optimized reaction condition for Diels-Alder reaction by utilizing MacMillan's imidazolidinone catalyst **1** and [bmim][NTf<sub>2</sub>] as the reaction solvent, we subsequently applied the optimized reaction condition to various substrates to explore the generality of the reaction system. As summarized in Table 3, entry 1–10, The Diels-Alder reaction involving various  $\alpha,\beta$ -unsaturated aldehydes and different cyclic dienes proceeded efficiently in the presence of MacMillan's imidazolidinone catalyst **1** in [bmim][NTf<sub>2</sub>],

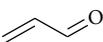
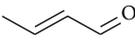
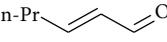
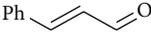
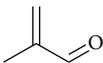
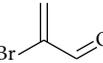
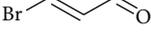
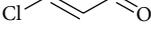
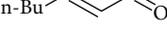
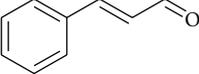
loading the corresponding products in good yield with excellent enantioselectivities. The comparable ee's were obtained in contrast to the use of imidazolidinone as a reaction catalyst which was previously reported by MacMillan and coworkers. For example, when *trans*-cinnamaldehyde was used as substrate, the utilization of MacMillan's imidazolidinone catalyst **1** affords the desired product in 93% ee. Likewise, by employing [bmim][NTf<sub>2</sub>] reaction solvent for MacMillan's imidazolidinone catalyst **1** in the Diels-Alder reaction almost similar results were achieved as well (Table 3, entry 10) [11].

With the success of the above reactions, we embark to test our modified protocol for the synthesis of steroids *via* Diels-Alder reaction, using complex open-chain diene and 7-methoxy-4-vinyl-1,2-dihydronaphthalene (Scheme 3) [18]. The cycloadduct **4** was obtained with a good enantiomeric excess (80%) and chemical yield (70%).

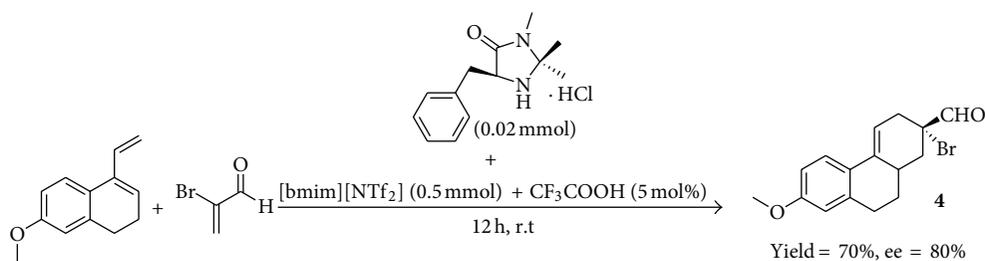
Next, we continued our study by exploring the recycling of MacMillan's imidazolidinone catalyst **1** for our model Diels-Alder reaction using [bmim][NTf<sub>2</sub>] as solvent (Scheme 4); after completion, the reaction product was extracted with ether. The MacMillan's imidazolidinone catalyst **1**/[bmim][NTf<sub>2</sub>] residue was dried under high vacuum at 50°C for 1 hour to facilitate the removal of volatile remnants prior to subsequent addition of the cyclohexadiene and acrolein in the next cycle (Scheme 4). The results are shown in Table 4.

It was noteworthy that the MacMillan's imidazolidinone catalyst **1** can be recycled for seven successive runs with comparable enantioselectivities and yields without loss of catalytic activity. Moreover, the extraction process was operationally simple, which offers easy product separation.

TABLE 3: [bmim][NTf<sub>2</sub>] mediated MacMillan's imidazolidinone catalyst **1** catalysed, Diels-Alder reaction of various dienes with dienophiles.

Entry	Diene	Dienophiles	Yield <sup>a</sup> (%)	<i>endo</i> : <i>exo</i> <sup>b</sup>	ee (%) <sup>c</sup>
(1)			98	19 : 1	97
(2)			90	1.5 : 1	92
(3)		n-Pr- 	97	3 : 1	96
(4)		Ph- 	85	1.5 : 1	97
(5)			95	49 : 1	98
(6)		Br- 	98	99 : 1	95
(7)		Br- 	99	1.1 : 1	78
(8)		Cl- 	88	1.1 : 1	88
(9)		n-Bu- 	90	1 : 1	89
(10)			99	1.2 : 1	92

<sup>a</sup>Isolated yield, <sup>b</sup>*endo*:*exo* ratio was determined by <sup>1</sup>H NMR crude reaction product, <sup>c</sup>ee% or was determined by HPLC or GC analysis.



SCHEME 3: Synthesis of steroids using the developed methodology.

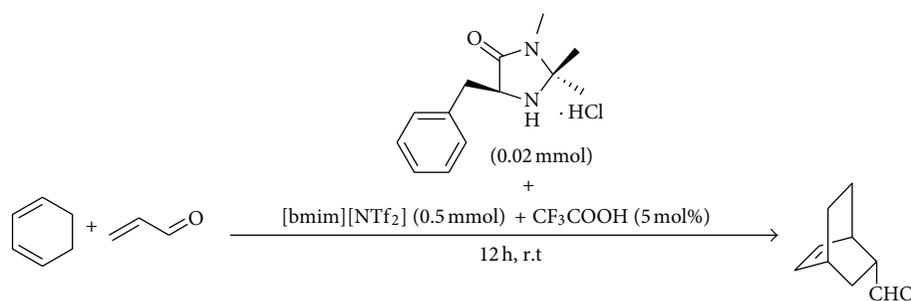
SCHEME 4: Recycling experiment for MacMillan's imidazolidinone catalyst **1**.

TABLE 4: Recyclability of MacMillan's imidazolidinone catalyst **1**/[bmim][NIF<sub>2</sub>] system.

No. of cycles	Yield (%) <sup>a</sup>	<i>endo</i> : <i>exo</i> <sup>b</sup>	ee (%) <sup>c</sup>
(1)	98	19:1	97
(2)	97	19:1	97
(3)	94	19:1	97
(4)	92	19:1	96
(5)	90	17:1	97
(6)	92	17:1	95

<sup>a</sup>Isolated yield, <sup>b</sup>*endo*:*exo* ratio was determined by <sup>1</sup>HNMR crude reaction product, <sup>c</sup>ee% or was determined by HPLC.

#### 4. Conclusion

In conclusion, we developed a modified and improved protocol for MacMillan's imidazolidinone catalyst **1** Diels-Alder reaction using ionic liquid as the reaction media and we successfully obtained enantiomerically enriched Diels-Alder adducts with high yields and selectivities. The main features of this reaction are as follows: (1) the procedure is operationally simple; (2) the cycloaddition adducts were obtained in good yield and selectivities for variety various dienes with dienophiles resulted in good yields and high selectivity. (3) We obtained the cycloaddition adduct with low catalyst loading (0.02 mmol instead of 0.036 mmol); (4) the catalyst can be recycled up to six cycles with comparable yields and selectivities. (5) Our modified protocol was found active in the synthesis of a tedious steroid **4** molecule.

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## Research Article

# Ultrasonic-Assisted Extraction of Procyanidins Using Ionic Liquid Solution from *Larix gmelinii* Bark

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An ionic liquid-based ultrasonic-assisted extraction method has been developed for the effective extraction of procyanidins from *Larix gmelinii* bark. So as to evaluate the performance of ionic liquids in ultrasonic-assisted extraction process, the effects caused by changes in the anion and the alkyl chain length of the cation on the extraction efficiency were investigated in this paper. The results indicated that the characteristics of anions had remarkable effects on the extraction efficiency of procyanidins, and 1-butyl-3-methylimidazolium bromide ([Bmim]Br) aqueous solution was the best among the investigated ionic liquids. The optimum conditions for the extraction were as follows: [Bmim]Br concentration 1.25 M, soak time 3 h, solid-liquid ratio 1 : 10, ultrasonic power 150 W, and ultrasonic time 30 min. This work not only introduces a simple, green, and highly efficient sample preparation method for extraction of procyanidins from *L. gmelinii* bark, but also reveals the tremendous application potential of ionic liquids.

## 1. Introduction

The procyanidins, one subclass of proanthocyanidins, consisting of (+)-catechin and/or (–)-epicatechin units are linked mainly through C4–C8 and/or C4–C6 bonds [1]. Procyanidins are important bioresources, which are the most abundant polyphenols in plants after lignins [2, 3]. Procyanidins have attracted attention in the fields of pharmacology and food chemistry because of their beneficial pharmacological effects such as radical scavenging [4], antioxidative [5], antiviral [6], antimicrobial [7], anticarcinogenic [8], and anti-inflammatory effects [9], as well as cardiotonic and antiarteriosclerotic activities [10, 11]. Because of their wide spectrum of pharmacological action, they are considered as functional ingredients in botanical and nutritional supplements [12]. Procyanidins are extracted from various natural sources, most notably apples, maritime pine bark, cinnamon, grape seed, and grape skin [13].

*Larix gmelinii* is a deciduous tree primarily distributed in northeast, China, north Sakhalin, and east Siberia. *L. gmelinii*

bark containing numerous procyanidins are extremely useful natural products. In recent years, procyanidins have been found in large quantities in *L. gmelinii* bark and have been recognized as a multipurpose natural component with great economic potential and environmental value, attracting the increasing attention of people [14–17].

The extraction of procyanidins from *L. gmelinii* bark has been accomplished by several extraction methods in the past. These include heating reflux extraction [15, 16] and homogenated extraction [17] with water, methanol, ethanol, acetone, acetic ether, and some mixtures as solvents [15–17]. However, the main disadvantage of traditional extraction lies in the complicated working procedure which increases the cost; repeated distillations prolong the heating time and accelerate oxidation of the extract. Moreover, these organic solvents used are problematic in the extraction of procyanidins because of their toxicity, volatility, and flammability. To overcome the above-mentioned problems, environment friendly techniques become attractive following the development of the “Green Chemistry.” Much wider attention has

been given to applications of ultrasound-assisted extraction (UAE) [18] and microwave-assisted extraction (MAE) [19, 20]. Among the two methods, UAE can more easily be scaled up for commercial production [18]. And the UAE is one of the promising extraction techniques that can offer high reproducibility in a shorter time, simplified manipulation, reduced solvent consumption and temperature, and lower-energy input, which has been widely used to extract analytes from many matrixes [21, 22]. Ultrasound enhancement of extraction is attributed to the disruption of cell walls, particle-size reduction, and the enhancement on the mass transfer of the cell content to the solvent caused by the collapse of the bubbles produced by cavitations [23, 24]. The UAE is expeditious, inexpensive, efficient, and an environmental protection alternative to conventional extraction techniques, which is also a well-established method in the processing of plant material and in the extraction of analytes from different parts of plants.

Ionic liquids, also known as molten salts, which are composed of organic cations and inorganic or organic anions, are liquid near room temperature (or by convention below 100°C) [25]. They have been proposed as greener alternatives to traditional organic solvents due to their unique characteristics such as good stability, negligible vapor pressure, wide liquidus range, good dissolving, and extracting ability, which have been attributed mainly to their nonmolecular nature [26–28]. In comparison with conventional organic solvents, ionic liquids could alleviate environmental pollution and improve the selectivity and the extraction efficiencies of compounds in separation technologies and sample pretreatment processes [29–33]. Ionic liquids as solvents are of promising potential in the application of the preparation of various useful substances from plant samples such as alkaloids [18, 19, 34, 35], stilbene [36], quinines [37], lignans [38, 39], and coumarins [40, 41]. As alternative solvents, the experimental results have indicated that ILs are promising solvents which are available in a simple and efficient technique for sample preparation and separation added in the introduction.

The aim of this work is to develop an effective, rapid, and environment friendly ionic liquid-based ultrasonic-assisted approach for the extraction of procyanidins from *L. gmelinii* bark and to compare the results with conventional extraction methods. Herein, we describe our investigations on the performance of various ionic liquids with different cations and anions in an ionic liquid-based ultrasonic-assisted extraction (ILUAE) method. It was found that parameters including the ionic liquid concentration, soak time, solid-liquid ratio, and ultrasonic power and time were influential on the extraction efficiency, and these parameters were optimized systematically.

## 2. Experimental

**2.1. Chemicals and Materials.** (+)-Catechin and (–)-epicatechin (with purity >98%) standards were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China), procyanidin dimers B2 [(–)-epicatechin-(4 $\beta$  → 8)-(–)-epicatechin] (with

purity  $\geq$ 90%) and trimer C1 [(–)-epicatechin-(4 $\beta$  → 8)-(–)-epicatechin-(4 $\beta$  → 8)-(–)-epicatechin] (with purity  $\geq$ 75%) were purchased from Sigma-Aldrich Inc. (St. Louis, USA), and B4 [(+)-catechin-(4 $\alpha$  → 8)-(–)-epicatechin] (with purity  $\geq$ 97%) was obtained from Tianjin Jianfeng Natural Product R&D Co., Ltd. All ionic liquids ([Emim]Br, [Bmim]Br, [Hmim]Br, [Omim]Br, [Dmim]Br, [Bmim]BF<sub>4</sub>, [Bmim]Cl, [Bmim]NO<sub>3</sub>, [Bmim]HSO<sub>4</sub>, [Bmim]OH, and [Bmim]Ac, where Ac = acetate; Emim = 1-ethyl-3-methylimidazolium, Bmim = 1-butyl-3-methylimidazolium, Hmim = 1-hexyl-3-methylimidazolium, Omim = 1-octyl-3-methylimidazolium, and Dmim = 1-decyl-3-methylimidazolium) were obtained from Chengjie Chemical Co. LTD. (Shanghai, China) and used without further purification. Acetonitrile used for HPLC analysis was of chromatographic grade and purchased from J&K Chemical Ltd. (Beijing, China) and used as received. Methanol, hydrochloric acid, vanillin and other reagents were all analytical grade and were obtained from Beijing Chemical Reagents Co. (Beijing, China). Reverse osmosis Milli-Q water (Millipore, Bedford, MA, USA) was used for all solutions and dilutions. All solutions and samples prepared for analysis were filtered through a 0.45  $\mu$ m nylon membrane (Guangfu Chemical Reagents Co., Tianjin, China).

*L. gmelinii* bark was provided by Mohe Forestry (Heilongjiang, China) and authenticated by Professor Shaoquan Nie from the State Engineering Laboratory for Bioresource Eco-Utilization, Northeast Forestry University, China. The bark was dried at room temperature for a month and then was powdered into a homogeneous size and then sieved (60–80 mesh). The same batch of samples was used here in the experiments.

**2.2. Ultrasonic-Assisted Extraction Apparatus.** For the ultrasonic-assisted extraction experiments, an ultrasonic bath was used as an ultrasonic source. KQ-250DB ultrasonic bath (Kunshan, Jiangsu, China) was used in the extraction step. The bath was a rectangular container (23.5 × 13.3 × 10.2 cm), to which 50 kHz transducers were annealed at the bottom. The bath power rating was 250 W on the scale of 40%–100%. The temperature control achieved by the replacement of inlet and outlet water to avoid water temperature rises.

**2.3. Ionic Liquid-Based Ultrasonic-Assisted Extraction.** 0.5 g of dried sample powder was mixed with 5 mL of the various ionic liquid aqueous solutions in a 25 mL flask. The flask was then partially immersed in the ultrasonic bath, which contained 2.5 L of water. The suspension was extracted by UAE. The cation and anion of the ionic liquid, concentration of selected ionic liquid, soak time, solid-liquid ratio, and ultrasonic power and time were systematically optimized in this work to obtain the best extraction efficiency. After each extraction, the extract was filtered through a 0.45  $\mu$ m nylon membrane (Guangfu Chemical Reagents Co., Tianjin, China) prior to the analysis. The extraction efficiency was expressed as the observed values of procyanidins, and the maximum amount in each curve was taken to be 100%.

**2.4. Reference and Conventional Extraction Method.** Pure water, 1.25 M sodium chloride, and 80% ethanol were selected for use as reference solvents in the UAE of procyanidins from *L. gmelinii* bark. The extraction experiments were operated under the optimized conditions except for solvent type. 0.5 g of sample powder was mixed with 5 mL of the above solvents and soaked for 3 h. The suspension was extracted for 30 min by UAE. Ultrasonic power and the solid-liquid ratio were 150 W and 1 : 10, respectively. The extract was filtered through a 0.45  $\mu\text{m}$  microporous membrane for analysis.

80% ethanol was selected as solvent in conventional heat reflux extraction (HRE) and maceration extraction (ME). The main technical parameters used were the same as above except extraction time and temperature 4 h and 85°C for HRE and 24 h and 25°C for ME, respectively.

**2.5. Vanillin-HCl Method Quantitative Analysis.** Procyanidins in the extract solution were determined by the standard vanillin-HCl method [42] using (+)-catechin as standard. Briefly, to 1.0 mL of the extract solution in a brown tube, 9.0 mL of 2% vanillin/HCl-methanol reagent (2 g vanillin dissolved in 12 N HCl-methanol (1 : 2) solution to get final volume of 100 mL) was added, immediately capped, mixed for 10 seconds, and incubated at 19–21°C for 15 min. Absorbance of this solution was measured by spectrophotometer (UV-2550, Shimadzu, Japan) at 500 nm (reference: water) ( $A_{\text{SOLUTION}}$ ). Procyanidins content was calculated from the value of ( $A_{\text{SOLUTION}}$ )-( $A_{\text{BLANK}}$ ) by using working curve.

Working curve was obtained as follows: 1, 2, and 3 mg of (+)-catechin was dissolved in water to a final volume of 10 mL (the standard solution). 1.0 mL of each standard solution was taken in a brown tube and 9.0 mL of 2% vanillin/HCl-methanol reagent was added, immediately capped, mixed for 10 seconds and incubated at 19–21°C for 15 min. Absorbance of this solution was measured at 500 nm by spectrophotometer (reference: water) ( $A_{\text{CAL}}$ ). In case of blank, water was used instead of standard solution ( $A_{\text{BLANK}}$ ). Working curve was obtained with correcting values: ( $A_{\text{CAL}}$ )-( $A_{\text{BLANK}}$ ). The working curve was constructed for procyanidins:  $Y = 0.0052x + 0.0164$ , ( $R^2 = 0.9974$ ), where  $Y = \text{Absorbance (Abs)}$  and  $x = \text{Concentration of reference substance } (\mu\text{g mL}^{-1})$ . A good linearity was found for absorbance in the range of 0.107 Abs–1.034 Abs.

**2.6. HPLC Qualitative Analysis.** The way ANOVA test was used to calculate the significance of the differences of extraction efficiency for the procyanidins. The results of spectrophotometric analysis were expressed as means of extraction efficiency  $\pm$  SD.

### 3. Results and Discussion

**3.1. Screening of the Ionic Liquid-Based Extracting Solvent.** The structure of ionic liquids had a significant influence on their physicochemical properties, which might have greatly affected the extraction efficiency of target analytes [43]. The

optimal ionic liquid for extraction was sought and the general trends observed are described below.

**3.2. Anion Effect.** Some papers indicate the important influence of the cation part in different properties. For the series of ionic liquids studied here, the water miscibility of the ionic liquid was important to the extraction efficiency. *N*-Methylimidazolium based ionic liquids with seven different anions ( $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{BF}_4^-$ ,  $\text{NO}_3^-$ ,  $\text{HSO}_4^-$ ,  $\text{Ac}^-$ , and  $\text{OH}^-$ ) were studied and differences in their extraction efficiency were readily apparent, as shown in Figure 1(a). All of the ionic liquids tested were sufficiently miscible in any proportion with water. The results showed that the ionic liquids based on  $\text{Br}^-$  and  $\text{HSO}_4^-$  were the more efficient of the liquids tested, with  $\text{Br}^-$  showing the best results. The hydrogen bonding and hydrophobic interactions of [Bmim]Br and [Bmim]HSO<sub>4</sub> caused the stronger solvation interactions with procyanidins. With the addition of ionic liquids, the extraction yields of procyanidins were improved greatly. This result indicates that extraction efficiency of procyanidins is anion dependent, which is similar to previous studies [43, 44].

**3.3. Effect of the Alkyl Chain Length of the Ionic Liquid Cation.** Using the same anion of  $\text{Br}^-$  a series of 1-alkyl-3-methylimidazolium cations including Emim<sup>+</sup>, Bmim<sup>+</sup>, Hmim<sup>+</sup>, Omim<sup>+</sup>, and Dmim<sup>+</sup> were evaluated, and the results are shown in Figure 1(b); the results implied that, for procyanidins, extraction efficiency increased slightly with the increasing alkyl chain length from ethyl to butyl. The alkyl chain length of cation was increased from butyl to dodecyl while the extraction efficiency decreased rather than increased. It could be attributed to the increase of the alkyl chain length in the cation moiety leading to larger steric clash. Having optimized both the anion and cation of the ionic liquid, [Bmim]Br was selected for subsequent extraction parameter optimization studies.

**3.4. Concentration Effect.** The optimum [Bmim]Br concentration in aqueous solution for UAE of procyanidins extraction was sought by carrying out extractions with [Bmim]Br solutions of different concentrations (from 0.25 to 1.25 M). Based on the results shown in Figure 1(c), it can be seen that the extraction efficiency increased in the [Bmim]Br concentration range of 0.25–1.25 M. We propose that the high viscosity of the solvent at high ionic liquid concentrations may lead to poor penetration of the solvent into the plant tissue and high ionic liquids consumption. 1.25 M [Bmim]Br solution was therefore selected as the optimal ionic liquid concentration.

**3.5. Optimization of the UAE Parameters.** The univariate method was used to optimize the following parameters: soak time, solid-liquid ratio, and ultrasonic power and time.

**3.5.1. Soak Time and Solid-Liquid Ratio.** Experiments were conducted by soaking the dry bark powder in the ionic liquid solution for 1, 2, 3, 4, or 8 h before UAE. Figure 2(a) shows the effect of soaking the sample powder in 1.25 M

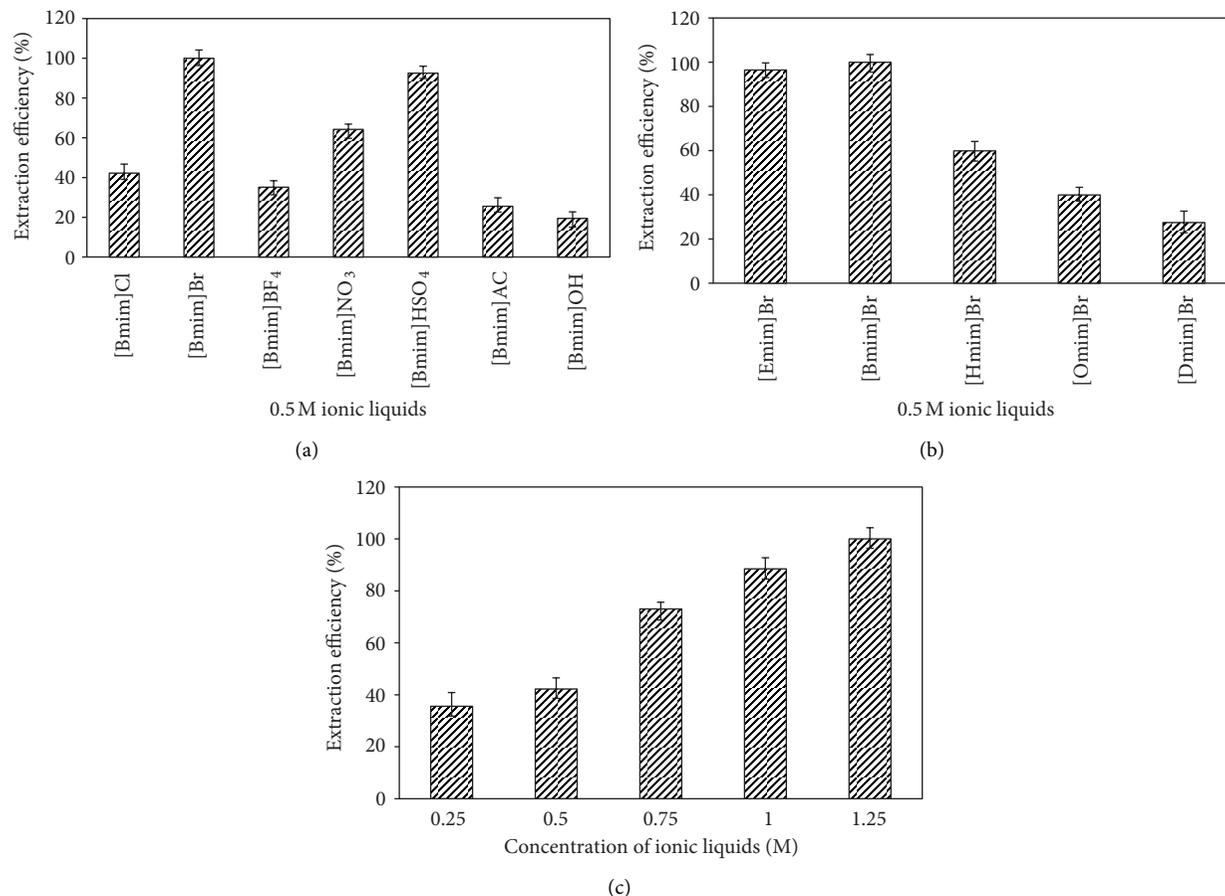


FIGURE 1: Effects of ionic liquids anions (a), cations (b), and concentration (c) on the extraction efficiency of target analytes. Sample: 0.5 g; extractant volume: 5 mL; soak time: 2 h; ultrasound power: 250 W; ultrasound time: 30 min; ionic liquid concentration: 0.5 M for (a) and (b). The extraction efficiency is expressed as the observed values of target analytes, and the maximum amount in each curve was taken to be 100%.

[Bmim]Br on the extraction of procyanidins from *L. gmelinii* bark at room temperature. It demonstrated the substantial increase in extraction efficiency obtained after soaking the bark. To extract procyanidins from the cellular structure, the solvent must have access to the cellular compartments, where the procyanidins are located. An intact cell structure restricts accessibility of the solvent to the procyanidins, while ultrasound treated cells have a more open, fragmented structure, which facilitates efficient extraction. The increase in extraction efficiency of the procyanidins after soaking with the solvent is probably because of increased diffusion of the solvent into the cellular structure allowing improved solubilization of the procyanidins. The extraction efficiency of procyanidins increased significantly when the soak time was 0–3 h, however; longer soak times did not lead to further increases in efficiency. Hence 3 h was chosen as the optimal soak time.

The solid-liquid ratio is a crucial factor and was also studied to optimize extraction efficiency. Large solvent volumes could make the procedure difficult and lead to unnecessary waste, while small volumes may lead to incomplete extraction. A series of experiments were carried out with different solid-liquid ratios (1 : 6, 1 : 8, 1 : 10, 1 : 12, and 1 : 14 g mL<sup>-1</sup>) to

evaluate the effect of the solid-liquid ratio. As shown in Figure 2(b), the extraction efficiency increased evidently with the increase of the solvent volume for solid-liquid ratio of up to 1 : 10. Higher solvent volumes, however, did not significantly improve the extraction efficiency. Thus, a solid-liquid ratio of 1 : 10 was adopted as the optimal solid-liquid ratio in this study.

**3.5.2. Ultrasonic Power and Time.** Ultrasonic power is believed to be the driving force for the complete dispersion of [Bmim]Br into the solid sample. To examine the effect of the ultrasonic power on the extraction efficiency, experiments were carried out at 100, 150, 200, and 250 W, respectively. The UAE time was maintained constant throughout this experiment at 30 min. Figure 2(c) shows the effect of ultrasonic power on extraction efficiency. With the ultrasonic power increasing from 100 to 150 W, the extraction efficiency of the procyanidins increased. However, when the ultrasonic power increased above 150 W, no obvious change could be observed at higher ultrasonic power. It meant that the ultrasonic power of 150 W was large enough to ensure the dispersion of [Bmim]Br. Thus, the ultrasonic power of UAE was set at 150 W in the following experiments.

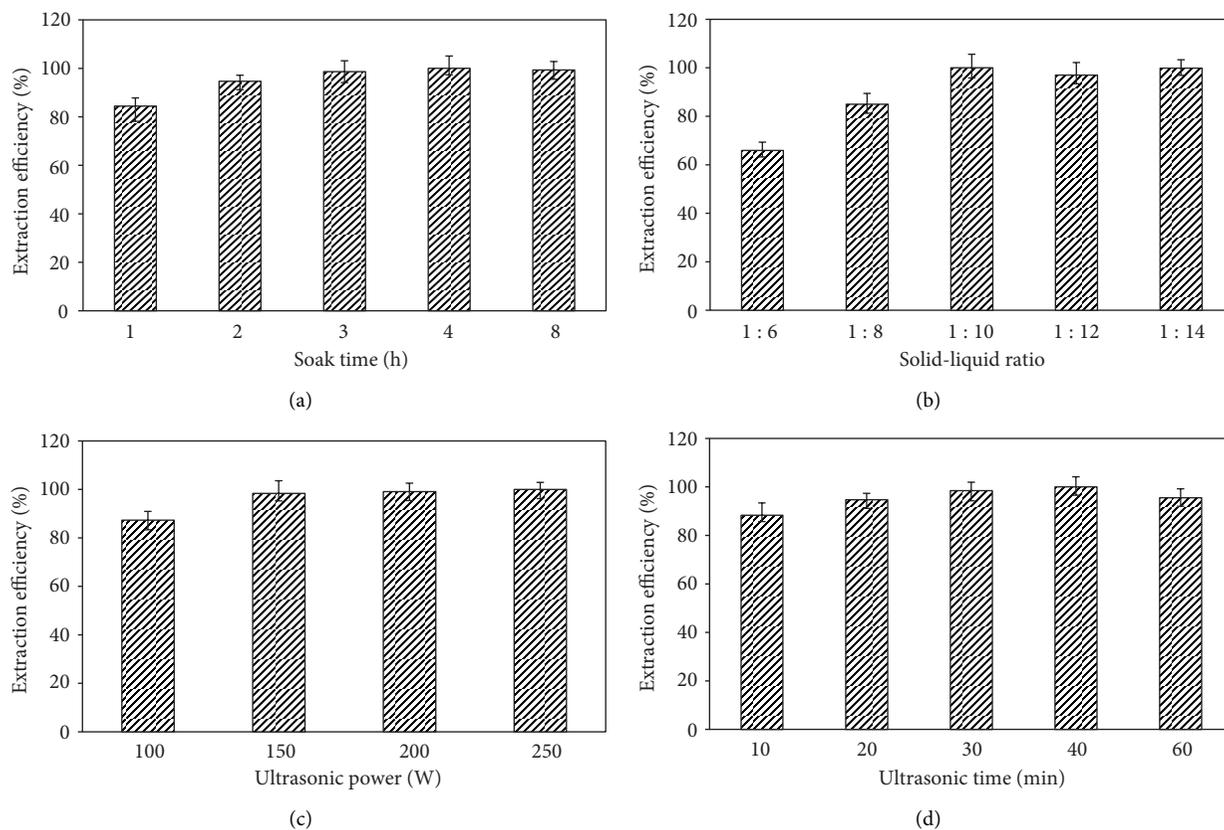


FIGURE 2: Optimization of extraction conditions: (a) 0.5 g of dried sample was mixed with 5 mL 1.25 M [Bmim]Br and then soaked for different times (1, 2, 3, 4, and 8 h) before the suspension was extracted for 30 min by UAE (250 W); (b) 0.5 g of dried sample was mixed with 1.25 M [Bmim]Br with different solid-liquid ratios (1:6, 1:8, 1:10, 1:12, and 1:14 w/v) and then soaked for 3 h before the suspension was extracted for 30 min by UAE (250 W); (c) 0.5 g of dried sample was mixed with 5 mL 1.25 M [Bmim]Br and then soaked for 3 h before the suspension was extracted for 30 min by UAE at different ultrasound powers (100, 150, 200, and 250 W); (d) 0.5 g of dried sample was mixed with 5 mL 1.25 M [Bmim]Br and then soaked for 3 h before the suspension was extracted for different times (10, 20, 30, 40, and 60 min) by UAE (150 W). The extraction efficiency is expressed as the observed values of proanthocyanidins, and the maximum amount in each curve was taken to be 100%.

The influence that the time ultrasonic was applied to the sample on the extraction efficiency of the alkaloids was examined over a range of 10 to 60 min, and the results are shown in Figure 2(d). They show that the extraction efficiency of procyanidins increased when the ultrasonic time was increased from 10 to 30 min. When the variable was changed from 30 to 60 min, slight improvements were observed. The extraction efficiency was low during the first 20 min of ultrasonication, indicating that more time was needed for ultrasound to disrupt the cell walls and aid the release of the procyanidins into the solvent. Prolonged application of ultrasound, of more than 30 min, did not result in any further significant improvement in extraction efficiency. It was found that more than 98% of the procyanidins content extracted during the first 30 min of UAE. The application of ultrasonic for 30 min was therefore selected for all subsequent experiments.

Reverse-phase HPLC was also used to analyze the composition of procyanidins. The HPLC apparatus was a Waters 717 automatic sample handling system series HPLC system (Waters Corporation, Milford, USA), consisting of a Waters 1525 bin pump with a steel column heater module controlling

the column temperature, and a Waters 2487 UV-detector monitored by a Waters Millennium 32 chromatography manager software. Chromatographic separation was performed on a HiQ sil-C18 reversed-phase column (4.6 mm × 250 mm, 5 μm, KYA TECH). The elution conditions were as follows: flow rate 1.0 mL min<sup>-1</sup>, column temperature 24°C, injection volume 10 μL, and solvent A: methanol, solvent B: 0.5% (v/v) phosphoric acid in water. The elution profile was: 0 min 18% A in B, 0–10 min 18% to 24% A in B, 10–15 min 24% A in B, 15–65 min 24% to 64% A in B, 65–75 min 100% A (wash-out), and 75–90 min 18% A in B (reconditioning). The detection wavelengths were set at 280 nm.

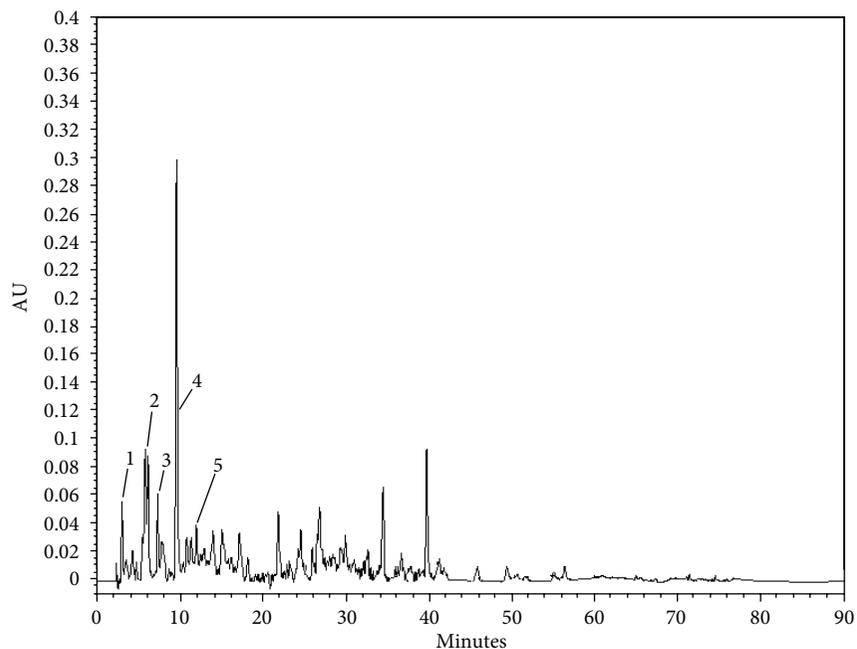
**3.6. Statistical Analysis.** Based on the above experiments, the optimum ultrasonic-assisted conditions were found to be: 1.25 M [Bmim]Br as extraction solvent, soak time of 3 h, solid-liquid ratio of 1:10 (w/v), ultrasonic power of 150 W, and extraction time of 30 min.

**3.7. Comparison of ILUAE Approach with the Reference and Conventional Methods.** The reference methods tested

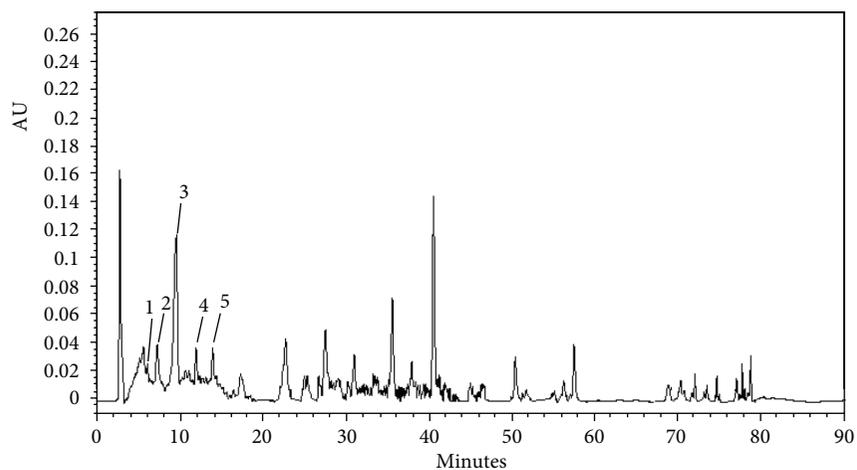
TABLE 1: Comparison of ILUAE with other extraction methods, mean  $\pm$  S.D. ( $n = 3$ ).

Number	Solvent	Extraction method	Time (h)	Solvent consumption ( $\text{mL g}^{-1}$ )	Temperature ( $^{\circ}\text{C}$ )	Extraction efficiency <sup>a</sup> $\pm$ SD (%)
1	Pure water	UAE	0.5	10	25	19.62 $\pm$ 0.76
2	1.25 M NaCl	UAE	0.5	10	25	17.47 $\pm$ 0.85
3	80% ethanol	UAE	0.5	10	25	67.10 $\pm$ 3.21
4	80% ethanol	ME	24.0	10	25	49.92 $\pm$ 2.51
5	80% ethanol	HRE	4.0	10	85	54.89 $\pm$ 2.66
6	1.25 M [Bmim] Br	UAE	0.5	10	25	100.00 $\pm$ 4.89

<sup>a</sup>The extraction efficiency is expressed as the observed values of procyanidins, and the maximum amount in each curve was taken to be 100%.



(a)



(b)

FIGURE 3: HPLC chromatogram recorded at 280 nm of procyanidins in an extract obtained using 1.25 M [Bmim]Br (a) and 80% methanol (b) as extraction solvent. Retention times (min): 1: B4; 2: B2; 3: (+)-catechin; 4: C1; 5: (-)-epicatechin.

included pure water extraction and sodium chloride solution extraction. Water is the most common and inexpensive solvent and is therefore often selected as a cosolvent in various extraction process. We compared the extraction capacities of ionic liquid solutions with pure water. As can be seen from Table 1, the extraction efficiency of the procyanidins was only  $19.62 \pm 0.76\%$  with water, while that obtained when using 1.25 M [Bmim]Br was  $100.00 \pm 4.89\%$ . The main contributor to procyanidins extraction efficiency was therefore the ionic liquid rather than water in the ionic liquid-water system. The procyanidins extraction efficiency achieved using 1.25 M NaCl solution was only  $17.47 \pm 0.85\%$ . The solvent effect of the ionic liquid was therefore more important in achieving high extraction efficiencies than the salt effect derived from NaCl. Hence, salt effects do not play a major role in improving the extraction of procyanidins.

In the present study, UAE, HRE, and ME techniques were compared for their efficiency in the extraction of procyanidins from *L. gmelinii* bark. The extraction efficiency of the procyanidins obtained under six different extraction methods using optimal conditions is summarized in Table 1. The extraction times used for UAE, HRE, and ME were 0.5, 4, and, 24 h, respectively. The extraction temperature of HRE was  $85^\circ\text{C}$ , while the extraction temperature used for UAE and ME was room temperature ( $25^\circ\text{C}$ ). The procyanidins extraction efficiency obtained using ILUAE methods was higher than those achieved using 80% ethanol HRE or ME methods.

**3.8. HPLC Qualitative Analysis.** The amount of the procyanidins studies presented in *L. gmelinii* bark extracts was qualitatively analyzed by using the chromatographic methodology. The chromatograms of HPLC of samples extracted with [Bmim]Br and 80% ethanol were shown in Figure 3. As can be seen from Figure 3, the relative contents of these characteristic procyanidin fraction ((+)-catechin, (-)-epicatechin, procyanidin dimers B2 and B4, and procyanidin trimer C1) in the [Bmim]Br extraction solution had improved distinctly, and [Bmim]Br had good effect on the extraction of procyanidins. It is clear that ILUAE represents an efficient method for the extraction of procyanidins from *L. gmelinii* bark.

## 4. Conclusions

In this work, we propose a novel extracting method for procyanidins from *L. gmelinii* bark based on the use of ionic liquids in UAE followed by Vanillin-HCl method analysis and quantification. The UAE conditions were optimized in detail. Considering the effect of both anion and cation, [Bmim]Br was selected for the subsequent evaluation. The optimum conditions for the extraction were as follows: [Bmim]Br concentration 1.25 M, soak time 3 h, solid-liquid ratio 1:10, ultrasonic power 150 W, and ultrasonic time 30 min. Under this condition, satisfactory extraction efficiency of the procyanidins was obtained. Relative to other methods, the proposed approach provided higher extraction efficiency and obviously reduced energy consumption time.

The method may also prove useful in the development of energy saving and environment friendly extraction methods for procyanidins from other plant materials.

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## Research Article

# Partitioning of Cephalexin in Ionic Liquid Aqueous Two-Phase System Composed of 1-Butyl-3-Methylimidazolium Tetrafluoroborate and ZnSO<sub>4</sub>

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Ionic liquid aqueous two-phase system (ILATPS) was applied in the extraction and separation of hydrosoluble antibiotics. The partitioning behavior of cephalexin (CEX) in 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF<sub>4</sub>)-ZnSO<sub>4</sub> aqueous two-phase system was studied by the partitioning parameter of the extraction efficiency. The effect of the volume of [Bmim]BF<sub>4</sub>, the concentration of ZnSO<sub>4</sub>, temperature, pH, and the volume of ZnSO<sub>4</sub> solution was discussed concretely. When the volume of [Bmim]BF<sub>4</sub> was 2 mL and the concentration of ZnSO<sub>4</sub> was 35%, the extraction efficiency of CEX could reach 92.64% with pH unadjusted. The effect of the volume of [Bmim]BF<sub>4</sub> on the extraction efficiency was higher than that of the concentration of ZnSO<sub>4</sub>. The temperature influenced not only the formation of aqueous two-phase system but also the extraction efficiency of CEX. The target was found to be preferentially extracted to the [Bmim]BF<sub>4</sub>-rich phase at the pH below 4.3. The partition of CEX to the top phase was enhanced by increasing the volume of [Bmim]BF<sub>4</sub>, the concentration of ZnSO<sub>4</sub>, and temperature; however, the partition of CEX to the top phase increased by decreasing the pH.

## 1. Introduction

For its gentle conditions, high biocompatibility and capacity and high extraction yield, aqueous two-phase extraction (ATPE), a novel liquid-liquid extraction technique, has been widely applied in the separation, concentration, and purification of biomolecules, such as proteins, nucleic acids, enzymes, antibodies, and antibiotics [1–6]. Aqueous two-phase system (ATPS) consists of two immiscible aqueous solutions including two incompatible polymers or one polymer and one salt above a certain critical concentration. The main problems of these polymer-based ATPSs are high viscosity of the polymer and the difficulty to isolate the extracted molecules from the polymer phase by back extraction.

In recent years, ionic liquids (ILs) composed of an organic cation and either an organic or inorganic anion have received more and more attention owing to their special features such as nonvolatility, nonflammability, good solubility, and

tunable physical and chemical properties. Some ILs can form ATPSs with concentrated solutions of salts, and these ionic liquid-salt aqueous two-phase systems (ILATPSs) have many advantages, such as low viscosity, gentle biocompatible environment which is much suitable for extraction of bioactive substance, short process time, and high extraction efficiency. Furthermore, proteins [7, 8], amino acids [9], polyphenolic compounds [10], anionic dyes [11], and biomolecules [12–14] have been successfully separated and concentrated by the ILATPSs.

Cephalexin (CEX, Figure 1) is hydrosoluble cephalosporins antibiotics. CEX is an amphoteric compound, and its isoelectric point was 4.3 [15]. The conventional methods currently used to extract CEX include liquid-liquid extraction [16], ultrafiltration [17], deproteination by organic solvent [18], solid-phase extraction [19, 20], and liquid membrane extraction [21, 22]. However, these traditional methods increase the total analysis time; using poisonous volatile

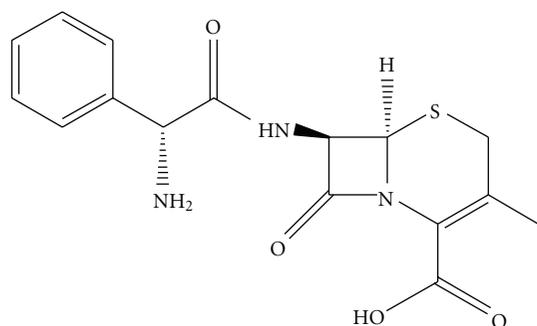


FIGURE 1: The structure of cephalexin (the isoelectric point,  $pI = 4.3$ ).

organic solvents or sample recovery is not always satisfactory. ATPE [23, 24], an alternative method, seems to be highly warranted from economic points of view. And in general, PEG-salt ATPS was employed for CEX extraction. Up to now, there have been few reports on using IL-based ATPS to extract CEX. Guo et al. [25] studied the partition of CEX by 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim] $BF_4$ )- $MgSO_4$  ILATPS. In this study, the feasibility of extracting CEX by [Bmim] $BF_4$ - $ZnSO_4$  ILATPS was first reported. In an acidic environment, the CEX was easy to be extracted to the [Bmim] $BF_4$ -rich phase. In this paper,  $ZnSO_4$ , an acid salt, was chosen as the phase-separation salt. The factors of the volume of [Bmim] $BF_4$ , the concentration of  $ZnSO_4$ , temperature, pH, and the volume of  $ZnSO_4$  solution affecting the partition of CEX were investigated.

## 2. Experimental

**2.1. Reagents and Instruments.** [Bmim] $BF_4$  was purchased from Chengjie Chemical Co., Ltd. (Shanghai, China) with a quoted purity of greater 0.99 mass fraction.  $ZnSO_4$  of analytical grade with a minimum mass fraction purity of 99.5% and methanol of HPLC grade were procured from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). The standard sample of cephalexin was obtained from the Chinese National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). All chemicals were used without further purification. The stock solution of CEX was prepared at a concentration of  $1000 \mu\text{g}\cdot\text{mL}^{-1}$  and stored at  $4^\circ\text{C}$  in a refrigerator. Standard working solutions of CEX were prepared by appropriately diluting the stock solution. All the solutions were prepared using deionized water throughout the entire experiments.

The BS124S electron balance (Beijing Sartorius instrument Co., Ltd., Beijing, China) was used for weighting. The pH was measured by a digital pH meter (Shanghai LIDA Instrument Factory, China). The Anke TDL-4 centrifuge (Shanghai, China) was used for centrifuging. The temperature was controlled by a thermostatic water bath (Henan, China). An Agilent 1200 HPLC (Agilent, USA) equipped with a quaternary pump and an ultraviolet-visible (UV) detector was used for analysis of extraction products. The

instrument control and data processing were actualized by using Agilent ChemStation software.

**2.2. Aqueous Two-Phase Extraction.** Aqueous two-phase extraction experiments were implemented by mixing the stock solutions of CEX and  $ZnSO_4$  in 10 mL graduated tubes. The concentrations of  $ZnSO_4$  studied were 20~46%, and the mass of CEX in it was  $100 \mu\text{g}$ . The pH of the mixed solutions was adjusted by adding hydrochloric acid and ammonia water into the stock solutions. Then different volumes of [Bmim] $BF_4$  (1~5 mL) were added to the above mixed solutions. After plenary mixing, the mixture was centrifuged at 2,000 rpm for 15 min and then placed into a thermostatic water bath at  $35 \pm 0.05^\circ\text{C}$  for 30 min to reach thorough phase separation. The volumes of the top and bottom phases were recorded precisely.

The partitions of CEX between the two phases were characterized by extraction efficiency ( $E$ ) and volume ratio ( $R$ ). The partitioning parameters were calculated by the following equations:

$$E = \frac{C_t V_t}{m_s} \times 100\% \quad (1)$$

$$R = \frac{V_t}{V_b}$$

where  $C_t$  was the equilibrium concentration of CEX in the top phase,  $m_s$  was the mass of CEX initially added, and  $V_t$  and  $V_b$  were the volumes of the top and bottom phases, respectively.

**2.3. Analytical Method.** After equilibrium was reached, the top phase was directly injected to HPLC without any treatment. An analytical reversed-phase column (Eclipse XDB-C18 column,  $250 \text{ mm} \times 4.6 \text{ mm}$ ,  $5 \mu\text{m}$ , serial no. G1314B) was used for chromatographic separations. The ratio of mobile phase of methanol and water was 23 : 77 at the flow rate of  $1.0 \text{ mL}\cdot\text{min}^{-1}$  and the column temperature of  $25^\circ\text{C}$ . The injected volume was  $20 \mu\text{L}$  and the column effluent was monitored at a wavelength of 261 nm. The calibration curve for CEX obtained in the range of  $0.10\sim 100 \mu\text{g}\cdot\text{mL}^{-1}$  was  $A = 26.1428284 \times C - 2.4398705$  ( $R = 0.99999$ ), where  $C$  was the concentration of CEX ( $\mu\text{g}\cdot\text{mL}^{-1}$ ) and  $A$  was the peak area.

## 3. Results and Discussion

**3.1. Effect of the Volume of [Bmim] $BF_4$  and the Concentration of  $ZnSO_4$ .** The extraction efficiency of CEX in [Bmim] $BF_4$ - $ZnSO_4$  ILATPS at different volumes of [Bmim] $BF_4$  and concentrations of  $ZnSO_4$  was listed in Figures 2 and 3. In Figure 2, different volumes of [Bmim] $BF_4$  were added to 3 mL CEX solutions containing different amount of  $ZnSO_4$ . When the volume of [Bmim] $BF_4$  was 1 mL, the minimal concentration of  $ZnSO_4$  which can form ATPS was 20%. When the concentration of  $ZnSO_4$  was 38% and the volume of [Bmim] $BF_4$  was higher than 3 mL, or when the concentration of  $ZnSO_4$  was 44% and the volume of [Bmim] $BF_4$  was greater than 2 mL, there was precipitation of  $ZnSO_4$  generated. The extraction efficiency of CEX was influenced by the combined

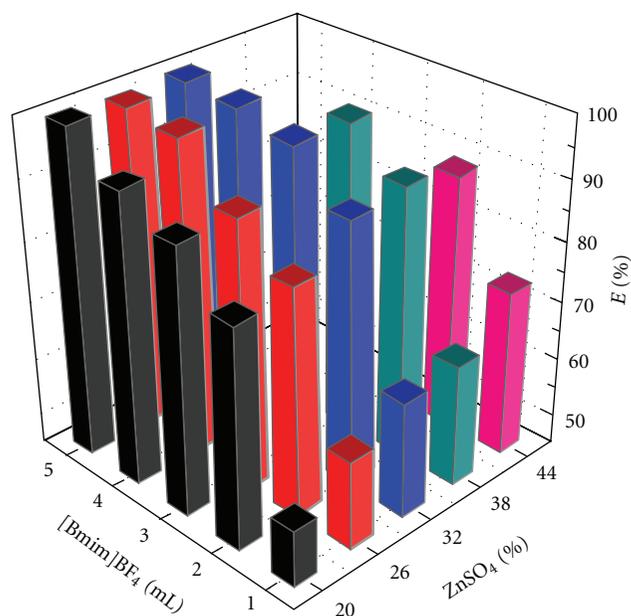


FIGURE 2: The influence of the volume of [Bmim]BF<sub>4</sub> on the extraction efficiency (*E*, %) of CEX at different concentrations of ZnSO<sub>4</sub>.

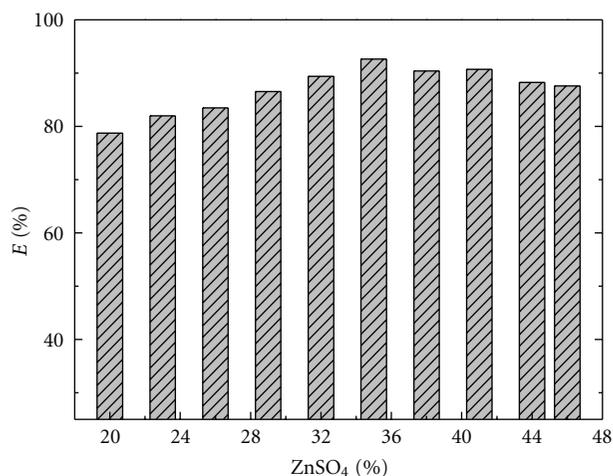


FIGURE 3: The influence of the concentration of ZnSO<sub>4</sub> on the extraction efficiency (*E*, %) of CEX.

impacts of the volume of [Bmim]BF<sub>4</sub> and the concentration of ZnSO<sub>4</sub>. When the volume of [Bmim]BF<sub>4</sub> was 3 mL and the concentration of ZnSO<sub>4</sub> was 20%, the extraction efficiency of CEX was about 90%; nevertheless, when the volume of [Bmim]BF<sub>4</sub> was 2 mL and the concentration of ZnSO<sub>4</sub> was 38%, the extraction efficiency of CEX has already reached 90%.

As shown in Figure 2, when the concentration of ZnSO<sub>4</sub> was a fixed value, the extraction efficiency of CEX increased with the volume of [Bmim]BF<sub>4</sub> increasing. The hydration between salt ions and water molecules leads to the phase-forming salt dissolving in the bottom phase; meanwhile, the amount of free water molecules in the bottom phase reduces,

and it results in the exclusion of [Bmim]BF<sub>4</sub> and target. The amount of water molecules in the [Bmim]BF<sub>4</sub>-rich phase rose with the increase of the volume of [Bmim]BF<sub>4</sub>, and due to the good water solubility of CEX, the amount of CEX which can transfer to the top phase also increased.

The impact of salt on the partition of CEX in the [Bmim]BF<sub>4</sub>-ZnSO<sub>4</sub> ILATPS is largely as a result of the salting-out effect of salt on the liquid-liquid equilibrium of ATPS. For instance, in Figure 2, when the volume of [Bmim]BF<sub>4</sub> was 1 mL, the extraction efficiency of CEX improved with the concentration of ZnSO<sub>4</sub> adding. Figure 3 showed the influence of the concentration of ZnSO<sub>4</sub> on the extraction efficiency of CEX when the volume of [Bmim]BF<sub>4</sub> was 2 mL. The extraction efficiency of CEX achieved the maximum value (92.64%) when the concentration of ZnSO<sub>4</sub> was 35%. Then with the growth in the concentration of ZnSO<sub>4</sub>, the extraction efficiency slightly decreased. Similarly, from Figure 2, when the volume of [Bmim]BF<sub>4</sub> was 2 mL or 3 mL, the extraction efficiency of CEX was obviously the same trend. When the salt solution reached equilibrium concentration in the bottom phase, redundant salt will remove to the top phase as salt concentration increased. The salt dissolving in the top phase combined with water molecules through hydration, so the amount of free water molecules in the top phase reduced, leading to a small part of CEX retransferring to the bottom phase. Therefore, high concentration of salt was not conducive to the extraction of the target. From Figures 2 and 3, when the concentration of ZnSO<sub>4</sub> was a fixed value and the volume of [Bmim]BF<sub>4</sub> was from 1 mL to 5 mL, the extraction efficiency of CEX obviously increased, especially when the volume of [Bmim]BF<sub>4</sub> was from 1 mL to 2 mL. However, when the volume of [Bmim]BF<sub>4</sub> was a fixed value, the growth of extraction efficiency of CEX slowly increased with the increase of salt concentration. So the effect of the volume of [Bmim]BF<sub>4</sub> on the extraction efficiency of CEX was greater than that of the concentration of ZnSO<sub>4</sub>.

**3.2. Effect of Temperature.** The influence of temperature on the extraction efficiency of CEX was discussed from 15°C to 55°C when the volume of [Bmim]BF<sub>4</sub> was 2 mL and the concentration of ZnSO<sub>4</sub> was 35%. After equilibrium reached, the changes of the volume of the top phase and the extraction efficiency of CEX were described in Figure 4. The extraction efficiency of CEX increased in the range of 15~35°C. The volumes of the [Bmim]BF<sub>4</sub>-rich phase always enlarged as the temperature rose, and it means that more and more water molecules were transferred to the top phase. Therefore, the extraction efficiency of CEX should have increased from 15°C to 55°C. But at the temperature of 45°C, the extraction efficiency began to decline. This was because the CEX was unstable at relatively high temperature. At 55°C, more CEX was decomposed, and the extraction efficiency of CEX decreased to 64%. It can be seen that the temperature is an essential factor affecting the partition of CEX in [Bmim]BF<sub>4</sub>-ZnSO<sub>4</sub> ILATPS.

**3.3. Effect of the Volume of ZnSO<sub>4</sub> Solution.** At the pH without adjusting, the influence of the volume of ZnSO<sub>4</sub>

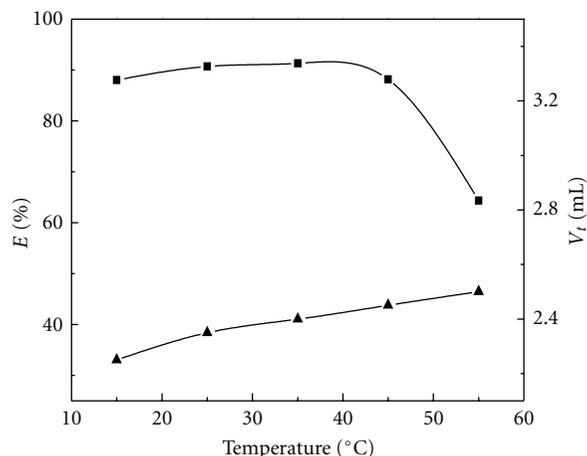


FIGURE 4: The influence of temperature on the extraction efficiency ( $E$ , %) of CEX and the volume of the top phase ( $V_t$ ): ■,  $E$  (%); ▲,  $V_t$  (mL).

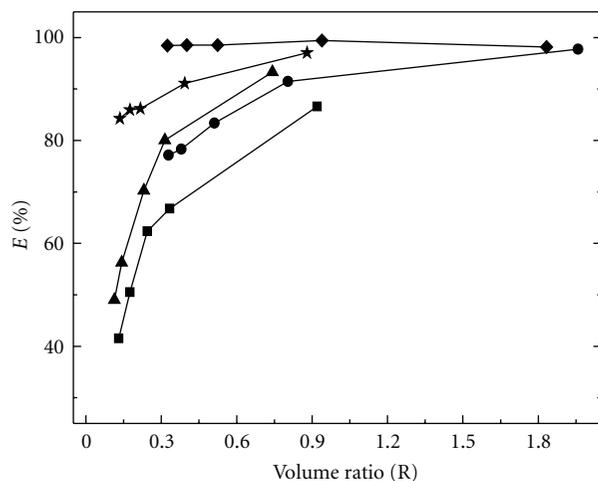


FIGURE 5: The influence of pH and the volume of  $\text{ZnSO}_4$  solution on the extraction efficiency ( $E$ , %) of CEX: square, 1 mL  $[\text{Bmim}]\text{BF}_4$  + 35%  $\text{ZnSO}_4$ ; circle, 2 mL  $[\text{Bmim}]\text{BF}_4$  + 35%  $\text{ZnSO}_4$ ; triangle, 1 mL  $[\text{Bmim}]\text{BF}_4$  + 46%  $\text{ZnSO}_4$ ; star, pH = 1, 1 mL  $[\text{Bmim}]\text{BF}_4$  + 35%  $\text{ZnSO}_4$ ; diamond, pH = 1, 2 mL  $[\text{Bmim}]\text{BF}_4$  + 35%  $\text{ZnSO}_4$ .

solution on the extraction efficiency of CEX was discussed. There were three ILATPSs, respectively, forming by different volumes of  $\text{ZnSO}_4$  solution in the same  $\text{ZnSO}_4$  concentration with the same volume of  $[\text{Bmim}]\text{BF}_4$ . In detail, the three ILATPSs were composed of 35%  $\text{ZnSO}_4$  + 1 mL  $[\text{Bmim}]\text{BF}_4$ , 35%  $\text{ZnSO}_4$  + 2 mL  $[\text{Bmim}]\text{BF}_4$ , and 46%  $\text{ZnSO}_4$  + 1 mL  $[\text{Bmim}]\text{BF}_4$  with 100  $\mu\text{g}$  CEX, respectively. From Figure 5, with the volume of the bottom phase (salt-rich phase) reducing, which also means the volume ratio increasing, the extraction efficiency of CEX always increased in the three ILATPSs. For example, when the volume of  $[\text{Bmim}]\text{BF}_4$  was 1 mL and the concentration of  $\text{ZnSO}_4$  was 35%, different volumes of  $\text{ZnSO}_4$  solution with 100  $\mu\text{g}$  CEX formed ATPSS by adding  $[\text{Bmim}]\text{BF}_4$ . The larger the volume of the bottom

phase is, the more water molecules it can get. Then CEX was more inclined to dissolve in the  $\text{ZnSO}_4$ -rich phase, and the extraction efficiency decreased.

**3.4. Effect of pH.** Cephalixin is an amphoteric compound possessing amino group and carboxyl group. The ionization states of CEX molecules vary with pH in the aqueous solution [26, 27]. It is positively charged below its isoelectric point of 4.3 and negatively charged above pH 4.3 [15]. The pH of  $\text{ZnSO}_4$  solutions is around 3.0. In this experiment, the pH from 1.0 to 5.0 was investigated. When the pH was adjusted to 6.0, there was sediment emerging in the bottom phase. The results showed that the extraction efficiency of CEX decreased from 99.31% to 91.22% at pH 1.0~4.0; then it immediately declined to 17.48% at pH 5.0. At pH values below 2.6, the predominant form of CEX was cationic. The interaction between the CEX cationic and  $\text{H}^+$  in the bottom phase was the mainly driving force for extraction. At pH < 2.6, almost all of the CEX was extracted to the top phase. Then with the pH rising, the extraction efficiency slightly descended. At pH 5.0 which is higher than the isoelectric point of CEX, it is negatively charged. And then it was more inclined to remain in the  $\text{ZnSO}_4$ -rich phase. In Figure 5, when the volume of  $[\text{Bmim}]\text{BF}_4$  was 1 mL, the extraction efficiency of CEX increased with the volume of  $\text{ZnSO}_4$  solution decreasing at pH 1.0. In comparison with the same ATPSS of unadjusted pH, the extraction efficiency of CEX at pH 1.0 was much higher when the volume ratio was similar. When the volume of  $[\text{Bmim}]\text{BF}_4$  was 2 mL, the extraction efficiency had little difference which was all greater than 98% at pH 1.0. So the lower the pH is, the higher extraction efficiency the CEX has.

## 4. Conclusions

In this paper, the  $[\text{Bmim}]\text{BF}_4$ - $\text{ZnSO}_4$  ILATPS was applied to separate hydrosoluble antibiotics and the partitioning behavior was discussed at great length. The distribution of CEX in the ILATPS was influenced by the volume of  $[\text{Bmim}]\text{BF}_4$ , the concentration of  $\text{ZnSO}_4$ , temperature, pH, and the volume of  $\text{ZnSO}_4$  solution. Without pH adjusted, the impact of  $[\text{Bmim}]\text{BF}_4$  and  $\text{ZnSO}_4$  on the extraction efficiency of CEX was as follows: the volume of  $[\text{Bmim}]\text{BF}_4$  > the concentration of  $\text{ZnSO}_4$ . CEX was preferentially extracted to the  $[\text{Bmim}]\text{BF}_4$ -rich phase at the pH below its isoelectric point of 4.3. At pH 1.0, the extraction efficiency of CEX increased with the increase of the volume of  $[\text{Bmim}]\text{BF}_4$  and the decrease of the volume of  $\text{ZnSO}_4$  solution; however, the extraction efficiency had little difference at different volumes of  $\text{ZnSO}_4$  solution when the volume of  $[\text{Bmim}]\text{BF}_4$  was 2 mL.

## Acknowledgments

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## Research Article

# 1-Methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium Chloride as a New and Green Ionic Liquid Catalyst for One-Pot Synthesis of Dihydropyrimidinones under Solvent-Free Condition

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An efficient and simple method for the preparation of 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride {(MSEI)Cl} as an acidic ionic liquid is described. One-pot multicomponent condensation of 1,3-dicarbonyl compounds, urea/thiourea and aldehydes at 80°C affords the corresponding compounds in high yields and in short reaction times by using (MSEI)Cl.

## 1. Introduction

First reported for multicomponent reaction involves a three-component, one-pot condensation of an aldehyde,  $\alpha,\beta$ -ketoester, and urea under strongly acidic conditions discovered by Biginelli in 1893 [10]. In the past few decades, interest in this reaction has increased dramatically since dihydropyrimidinones have a wide range of biological activities, acting as calcium channel antagonists, anti-hypertensive, anti-bacterial and anti-inflammatory agents, while also possessing cytotoxic activity [11–17]. In order to improve the efficiency of Biginelli reaction, a variety of catalysts have been reported which of them  $H_4PMo_{11}VO_{40}$ , [18], Dowex-50W [19],  $H_3PW_{12}O_{40}/SiO_2$  [20],  $MgBr_2$  [21], polymer-supported 4-aminoformoyldiphenylammonium triflate [22],  $NaHSO_4/SiO_2$  [23],  $FeCl_3$  [24],  $ZrCl_4$  [25],  $Cu(OTf)_2$  [26],  $Bi(OTf)_3$  [27], ytterbium triflate [28],  $NH_2SO_3H$  [29], 12-Molybdophosphoric acid [30], natural HEU type zeolite [31],  $Sr(OTf)_2$  [32], covalently anchored sulfonic acid onto silica [33],  $ZrOCl_2 \cdot 8H_2O$  [34], silica triflate [35],  $Fe(HSO_4)_3$  [36], TCICA [37],  $PPh_3$  [38],  $CaF_2$  [39], [bmim] $BF_4$ -immobilized Cu(II) acetylacetonate [40], [bmim][ $FeCl_4$ ] [7], ionic liquid-sunder ultrasound irradiation [41], and melamine trisulfonic acid [42] are examples. Ionic liquids (ILs), which have been widely promoted as green solvents, are attracting much attention for applications in many fields of chemistry and industry due to their chemical and thermal stability, low

vapor pressure, and high-ionic-conductivity properties. Over the last few years, ILs have been popularly used as solvents for organic synthesis, catalysis, and also been used as media for extraction processes [43, 44]. But some of the mentioned methods encounter drawbacks such as the requiring expensive reagents, long reaction times, low yields of the products and tedious workup. The advantages of the present procedure are simplicity of operation, short reaction times, inexpensive reagents, green condition, and the high yields of products.

We synthesized the bronsted acidic ionic liquid 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride [45] as an efficient and reusable catalyst for the synthesis of DHPMs derivatives.

## 2. Experimental

IR spectra of the compounds were obtained on a PerkinElmer spectrometer version 10.03.06 using a KBr disk. The  $^1H$  nuclear magnetic resonance ( $^1H$  NMR) spectra were recorded on a Bruker AQS 400 Avance instrument at 400 MHz in dimethyl sulfoxide ( $DMSO-d_6$ ) using tetramethylsilane as an internal standard. The progress of reaction was followed with thin-layer chromatography (TLC) using silica gel SILG/UV 254 and 365 plates. All the products are known compounds and were characterized by comparing the IR,  $^1H$  NMR, and  $^{13}C$  NMR spectroscopic data and their melting points with the literature values.



TABLE 1: Temperature and time effect on dihydropyrimidinones synthesis.

Entry	Temperature (°C)	Time (min)	Yield (%)
1	r.t.	90	36
2	50	90	45
3	80	30	93
4	100	30	91
5	120	30	90

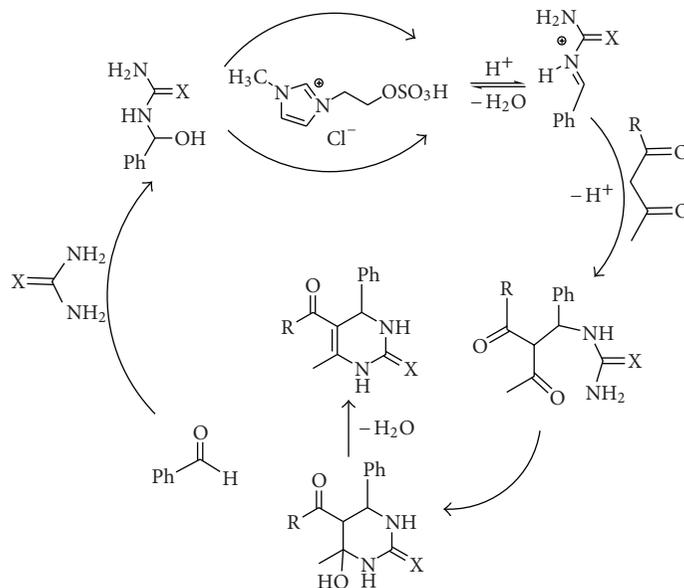
TABLE 2: Dihydropyrimidinones synthesis catalyzed by Brønsted acidic ionic liquid (BAIL).

Entry	R <sub>1</sub>	R <sub>2</sub>	X	Time (min)	Yield (%)	M.p. (°C)	
						Found	Reported
1	Ph	Me	O	30	93	231–233	235–236 [1]
2	4-OH-C <sub>6</sub> H <sub>4</sub>	Me	O	30	95	254–256	256–258 [2]
3	4-Me-C <sub>6</sub> H <sub>4</sub>	Me	O	30	92	231–232	228–229 [1]
4	4-MeO-C <sub>6</sub> H <sub>4</sub>	Me	O	30	90	175–177	177–179 [2]
5	4-Cl-C <sub>6</sub> H <sub>4</sub>	Me	O	30	92	223–224	224–226 [3]
6	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Me	O	45	85	227 (dec)	229 (dec) [2]
7	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Me	O	45	82	246–248	248–250 [1]
8	Ph	OEt	O	45	88	203–205	201–202 [1]
9	2-OH-C <sub>6</sub> H <sub>4</sub>	OEt	O	45	92	200–202	201–203 [3]
10	4-Me-C <sub>6</sub> H <sub>4</sub>	OEt	O	45	90	170–172	170–171 [1]
11	4-MeO-C <sub>6</sub> H <sub>4</sub>	OEt	O	45	87	198–200	199–201 [4]
12	4-Cl-C <sub>6</sub> H <sub>4</sub>	OEt	O	45	86	211–213	209–210 [1]
13	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	OEt	O	60	78	225–227	226–227 [4]
14	Ph	Me	S	75	81	230–231	232–233 [5]
15	2-OH-C <sub>6</sub> H <sub>4</sub>	Me	S	75	83	239–241	242–243 [3]
16	4-Me-C <sub>6</sub> H <sub>4</sub>	Me	S	75	80	221–223	222–224 [5]
17	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Me	S	90	73	106–107	108–110 [6]
18	Ph	OEt	S	105	75	206–208	208–209 [5]
19	4-Me-C <sub>6</sub> H <sub>4</sub>	OEt	S	105	72	193–194	193–194 [1]
20	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	OEt	S	120	70	214–216	209–212 [3]

TABLE 3: Comparison of catalytic ability of catalysts.

Entry	Catalyst	Time (min) condition	Yield (%) (reference)
1	[BMIM]FeCl <sub>4</sub>	120 90°C, s.f. <sup>a</sup>	90 [7]
2	[HMIM]Tfa	45 50°C, s.f.	90 [4]
3	[BMIM]BF <sub>4</sub>	30 100°C, s.f.	99 [8]
4	[HMIM]HSO <sub>4</sub>	90 80°C, s.f.	96 [9]
5	[MSEI]Cl	30 80°C, s.f.	93 —

<sup>a</sup>s.f.: solvent free condition.



SCHEME 3: Mechanism of synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones.

TABLE 4: Formation of DHMP in different solvents and comparison with solvent-free condition.

$$\text{PhCHO} + \text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}_2 + \text{Me}-\text{C}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})-\text{Me} \xrightarrow{\text{BAIL}} \text{Product}$$

Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	Ethanol	4	Refluxing	81
2	H <sub>2</sub> O	4	Refluxing	<20
3	MeCN	4	Refluxing	70
4	CH <sub>2</sub> Cl <sub>2</sub>	8	Refluxing	38
5	Solvent-free	0.5	80	93

TABLE 5: Recovery of catalyst.

Number	Reaction	Yield (%)
1	First	91
2	Second	91
3	Third	90
4	Forth	88

**2.1. Preparation of Bronsted Acidic Ionic Liquid.** 1-Methylimidazole **1** (4.1 g, 50 mmol) and 2-chloroethanol **2** (4.02 g, 50 mmol) were added in a flask containing 10 mL of CHCl<sub>3</sub>, and the mixture was refluxed for 8 h and removed CHCl<sub>3</sub> under vacuum. Unreacted 1-methylimidazole or 2-chloroethanol was extracted with ether (3 × 10 mL) to give 1-methyl-3-(2-hydroxyethyl) imidazolium chloride (yield 95%). IR spectrum of compound **3**: OH (3200–3600 cm<sup>-1</sup>), C=C (1450, 1575 cm<sup>-1</sup>), and C=N (1643 cm<sup>-1</sup>) (Figure 2).

A stoichiometric amount of 97% chlorosulfonic acid (3.4 mL, 50 mmol) in CCl<sub>4</sub> (10 mL) was added dropwise to

compound **3** over a period of 45–60 min at 0°C, and HCl gas was evolved in an alkali trap immediately (Scheme 1). The mixture was washed with CCl<sub>4</sub> (3 × 10 mL) to remove the unreacted chlorosulfonic acid (yield 92%). IR spectrum of compound **4**: OH (3200–3600 cm<sup>-1</sup>), C=C (1440, 1579 cm<sup>-1</sup>), C=N (1648 cm<sup>-1</sup>), S=O (1019 cm<sup>-1</sup>), and S–O (623 cm<sup>-1</sup>) (Figures 1 and 2) [44].

**2.2. General Procedure for the Preparation of DHPMs.** A mixture of an aromatic aldehyde (1 mmol), β-dicarbonyl (1 mmol), urea/thiourea (1.5 mmol), and catalyst (50 mg) was finely mixed together in a test tube at 80°C for the times reported in (Table 2). During the reaction process, a solid product spontaneously formed. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and then cold water (20 mL) was added to the reaction mixture and stirred for 10–15 min. During this time, crystals of the product formed which were collected by filtration and dried and then recrystallized

from ethanol to afford the pure product. The results are summarized in Table 2. The aqueous layer (including BAIL) was separated, and its solvent was evaporated to obtain pure BAIL. The recycled catalyst was used for the next run under identical reaction conditions.

### 3. Results and Discussion

The one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones was achieved by the three-component condensation of aldehydes, dicarbonyl, and urea or thiourea in presence of bronsted acidic ionic liquid is conducted at 80 °C, and the results are summarized in Table 1. The procedure gives products in good yields, short reaction times and avoids the use of organic solvents (handling, cost, safety, pollution) (Table 4). Environmental friendly ionic liquid afforded a valuable alternative to promote a numerous efficient catalytic systems that have already been proposed for the achievement of DHPMs. As long as, the reaction rate and the yields are depending on electron donating/withdrawing effect of the groups on the benzene ring in benzaldehydes. Aryl aldehydes containing electron-donating substituent gave excellent yields of the products in a shorter reaction time. The mechanism of the Biginelli reaction established by Kappe [6] proposed that the key step in this cyclocondensation process should involve the formation of N-acyliminium ion intermediate (Scheme 3).

According to Table 2 the using of thiourea and ethylacetoacetate increased reaction time, and also the using of thiourea reduces the efficiency of Biginelli reaction. Thiourea stability of negatively charged than urea and low nucleophiles property of thiourea than urea at intermediate state. The catalyst is reusable and can be applied several times without any decrease in the yield of the reaction. As it can be seen from Table 3, (MSEI)Cl as a catalyst afforded the good results with respect to the another ionic liquid catalysts.

### 4. Conclusions

In summary, we have developed the use of bronsted acidic ionic liquid 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride as an inexpensive, easy to handle, noncorrosive and environmentally benign catalyst for the Biginelli reaction from an aldehyde, a  $\beta$ -dicarbonyl, and urea or thiourea. The advantages of the present procedure are simplicity of operation, very short reaction times compared with other procedures for the preparation of dihydropyrimidinones derivatives, and the high yields of products. In this reaction the catalyst can be easily recyclable after removing starting materials and water (Table 5).

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