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Zwitterionic HBr carriers for the synthesis of 2-bromopropionic acid from lactide

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Abstract

A convenient and highly efficient way of synthesizing 2-bromopropionic acid (2-BrPA) from lactide is presented. The procedure uses ionic liquids obtained from the addition of HBr to ammonium-based zwitterions as solvent and bromination agent. The buffered HBr acidity, high polarity, and charge stabilizing character of the IL enable 2-BrPA synthesis with excellent selectivity. The best results were obtained with the imidazolium-based IL 1-(4-butane sulfonic acid)-3-methyl imidazolium bromide ([MIMBS]Br). It was found that adjustment of the right HBr loading and the water content of the IL are crucial parameters for the bromination reaction. The formed 2-BrPA product can be selectively isolated *via* extraction from the IL and the unconverted substrate remains in the [MIMBS]Br for the next run. Successful recycling of the IL over four cycles was demonstrated.

Keywords

2-bromopropionic acid, lactide, lactic acid, renewable resources, ionic liquids, zwitterions, bromination, acrylic acid

Introduction

Bromo-organic compounds are used in diverse chemical reactions like bromination^[1], oxidations^[2], hydrolysis^[3], substitutions^[4], or catalysis^[5] and are therefore involved in the synthesis of complex organic molecules, e.g. in the polymer, pharmaceutical, and agrochemical industries.^[6] Due to their acidity, reactivity, and distinct biological properties^[7], halogenated carboxylic acids (HCAs) are typically used as alkylation and acylation reagents in the chemical industry^[8]. 2-Bromopropionic acid, a bromo-derivative of the above mentioned HCA-group, is used for example in the synthesis of triazole derivatives^[9], which have attracted tremendous interest among organic and medical chemists owing to their remarkable and wide range of biological activities.^[10]

In addition, a recent publication by Terrade et al.^[11] in this journal as well as contributions from Wasserscheid et al.^[12] have added a new and highly relevant field to the group of technically interesting applications of 2-BrPA. These authors have reported a novel method for the production of bio acrylic acid (bio-AA) from fermentatively produced lactide/lactic acid derivatives. Terrade et al. described a catalytic cracking of lactide in bromide salts in the presence of a strong acid. This novel process is very different from the previously described processes to bio-AA from lactic acid (LA) feedstocks, as the described reaction is a rearrangement of lactide and not a dehydration of LA. Moreover, the reaction is performed in the liquid phase at significantly lower temperatures (130 – 175°C)^[11] compared to the typical gas-phase process conditions (300 – 500°C).^[13] Alternative feedstocks for this liquid-phase process for bio-AA production include LA oligomers and LA polymers. The proposed mechanism of lactide cracking proceeds *via* brominated LA-species and involves a S_N2 / elimination sequence, forming AA from 2-BrPA, for example. Terrade et al. describe in reference [11] and the related patent literature^[14] AA yields of up to 58% obtained from lactide after 10 h at 175°C (the reaction mixture included 0.69 mmol lactide, 0.83 eq. of anhydrous methanesulfonic, 5 eq. of tetraphenylphosphonium bromide, and sulfolane). While this is a remarkable and highly interesting result, the economics of such an alternative process for bio-AA production from biomass-derived lactide would largely improve if higher yields are achieved. An obvious approach toward this important goal is to split the reaction sequence in accordance with the claimed mechanism in two steps, namely a highly selective 2-BrPA synthesis from LA derivatives and a highly selective dehydrobromination of 2-BrPA to AA. While the first step requires high HBr concentrations and modest temperatures in order to prevent the decomposition of the lactide over the carbocation to acetaldehyde and CO, the second step is promoted by low HBr pressure and basic conditions. From these considerations, we anticipate that there will be a strong interest in the future in selective 2-BrPA synthesis from lactide in the context of liquid-phase routes to bio-AA. This could make 2-BrPA a relevant intermediate for acrylic acid production (world-wide production ca. 5 Mio tons/year^[15] and rising tendency) to enable a bio-based industrial production of the corresponding coatings, plastics, and superabsorbers.^[15b, 16]

Currently, 2-BrPA is produced *via* the *Hell-Vollhard-Zelinsky*^[17] reaction from mainly crude-oil-based propanoic acid (PA). In this reaction, PA is processed with phosphorous tribromide and elemental

bromine under elevated temperatures forming considerable amounts of waste by-products. By all accounts, this process does not include green and sustainable process conditions.

A much more suitable substrate for a sustainable production of 2-BrPA is LA which is commercially produced by fermentation of sugar. LA is already used as safe and bio-based chemical in the food industry and for the production of the biodegradable polymer polylactic acid (PLA). The expected drop in LA cost, resulting from an expected increase in production capacity and improved manufacturing technology, will make LA an even more attractive starting material in the future.^[18]

Recently, ionic liquids (ILs) have attracted the interest of the scientific community due to their well-known and interesting properties, offering immense opportunities as, for example, catalysts and novel solvents for chemical transformations.^[19] Among the reported ionic liquid-based innovations, new methods for the halogenation of alcohols and diols appear particularly promising because halide ILs have been reported as excellent halogenating agents acting at the same time as solvents and vapor pressure reducing agents for the applied or formed hydrogen halide acids.^[20] These methods can overcome some disadvantages of traditional bromination methods for alcohols, including corrosive and toxic halogenation agents, difficult product separation, and low atom economy.^[21] For instance, BASF^[22] (chlorination of butane-1,4-diol) and SOLVAY^[23] (hydrochlorination of acetylene) already apply ILs in industrial halogenation processes.

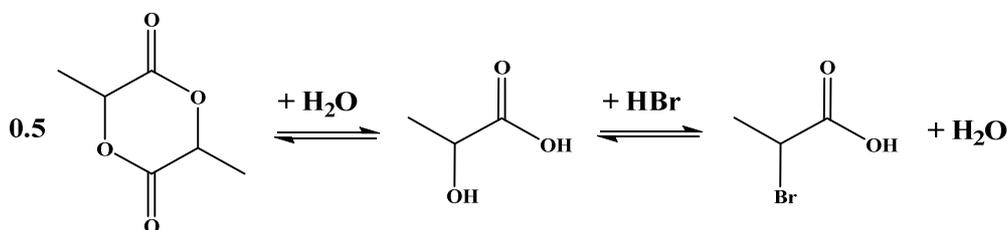
In 2011, Li et al.^[24] reported the use of a zwitterionic HBr-carrier system as bromination medium for 1,7-heptanediol. In that work, the bromide salt resulting from the addition of HBr to the zwitterion acts as catalyst, brominating agent, and solvent.^[24] More importantly, the applied HBr is chemically bound to the zwitterion which greatly reduces HBr vapor pressure and makes the system relatively easy to handle. In the present contribution, we transfer this methodology to the bromination of functionalized and much more sensitive bio-based substrates, such as lactic acid and lactide. We show that different zwitterions can be successfully applied as HBr carriers to enable highly selective bromination of LA to 2-BrPA. We report on the development of an optimized reaction protocol using the ionic liquid 3-methyl-1-(4-butane sulfonic acid) imidazolium bromide ([MIMBS]Br) and demonstrate the excellent recyclability of the IL in this challenging bromination reaction.

Results and Discussion

Aqueous media results

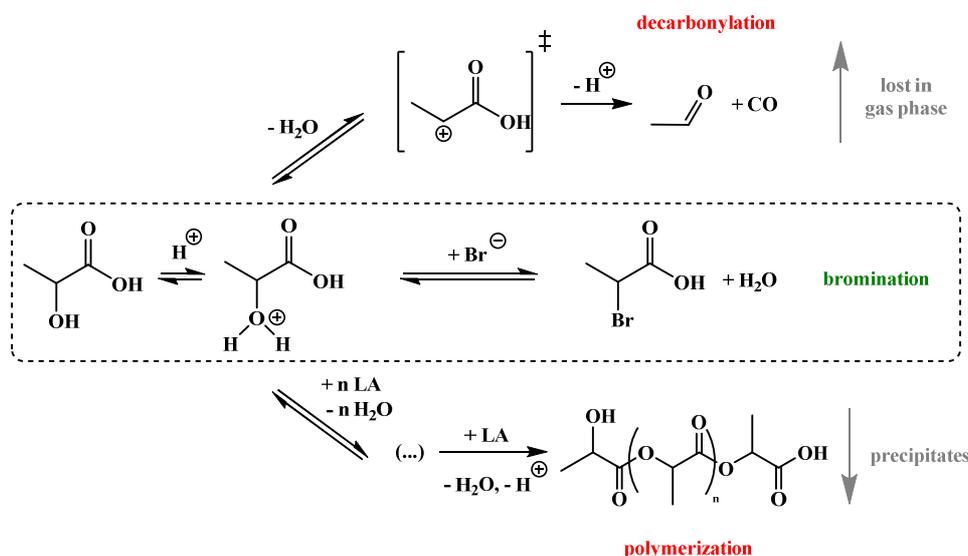
In principle, 2-BrPA can be made from LA *via* nucleophilic substitution of the hydroxyl group by bromide. A typical protocol would include refluxing the alcoholic substrate with aqueous hydrobromic acid (HBr_(aq))^[25]. Indeed, the formation of 2-BrPA from LA and HBr_(aq) has been first described in 1864 by Kekulé.^[26] In our first experiments, we applied lactide to form 2-BrPA in the presence of HBr_(aq) at elevated temperatures (see Scheme 1). Lactide can be seen as two lactic acid (LA) equivalents and was

used as an alternative substrate because it does not contain water. Fast lactide hydrolysis and consequently LA formation was observed in aqueous HBr solution and even in bromination media with lower water content (zwitterion-based HBr carriers). Heating the reaction mixture to 110 °C for 5 s caused formation of 2-BrPA from lactide as proven *via* ^1H NMR spectroscopy (see Supporting Information).



Scheme 1: Observed reaction mechanism of lactide in $\text{HBr}_{(\text{aq})}$ at elevated temperatures.

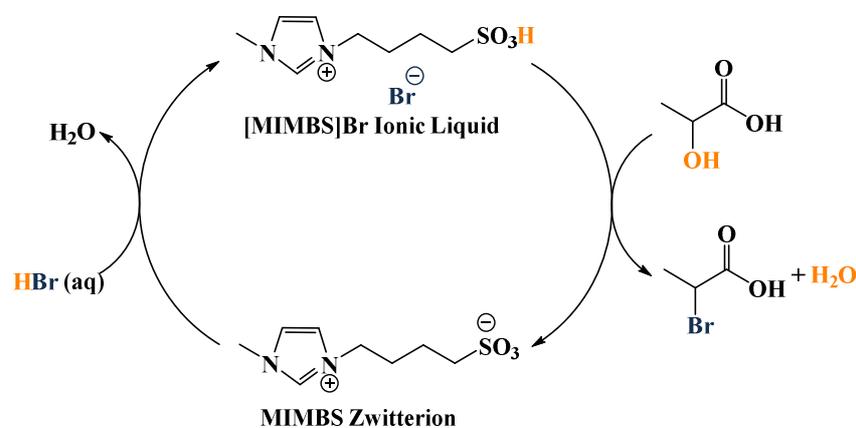
However, it is challenging to produce 2-BrPA from LA derivatives and $\text{HBr}_{(\text{aq})}$ in high selectivity as substrate decarbonylation and self-oligomerization / polymerization reactions predominate. The postulated reaction network of the aqueous bromination system is shown in Scheme 2. Enormous mass loss over longer reaction times and significant evolution of gas above reaction temperatures of 100 °C result from the strongly competing decarbonylation pathway. Gaseous by-products (acetaldehyde and carbon monoxide) were detected in our set-up by off-gas analysis. Polymerization has been verified by precipitation of black and amorphous solid. Even under optimized reaction conditions, namely 5 h, 120 °C, and a molar ratio of LA:HBr = 1:3, selectivity towards 2-BrPA ($S_{2\text{BrPA}}$) was below 50%. Note, that both decarbonylation as well as (poly)condensation produce stoichiometric amounts of water, which when added to the water in the aqueous bromination agent ($\text{HBr}_{(\text{aq})}$, 48 wt% in water), limit the equilibrium conversion to 2-BrPA. Under optimized conditions, the yield of 2-BrPA ($Y_{2\text{BrPA}}$) that could be realized was approximately 25%.



Scheme 2: Postulated reaction network in the aqueous reaction medium showing the desired bromination (mid) and both side-reactions, namely substrate decarbonylation (top) and polymerization (bottom).

To overcome the limitations of LA bromination with $\text{HBr}_{(\text{aq})}$, we decided to investigate ammonium-based zwitterions as HBr carriers and brominating agents.^[23] The applied zwitterionic carrier molecule is loaded with HBr by protonation of the sulfonate group, thus forming an acidic bromide IL. This IL-based bromination system provides several benefits compared to $\text{HBr}_{(\text{aq})}$: The bromide anion of the acidic bromide IL appears to be more nucleophilic than that in pure HBr ^[23]. Furthermore, due to the drastically reduced H_2O content of the brominating agent, the formation of 2-BrPA that releases water as coupling product should be significantly increased. Another very attractive feature of protonated zwitterion bromides is the low vapor pressure of HBr in these systems allowing for a safe handling of HBr at elevated temperatures. Thus, the zwitterionic HBr carriers combine the roles of solvent, proton source, buffer, and brominating agent within one substance.

The general concept of applying SO_3H -functionalized bromide ionic liquids for a convenient and efficient production of 2-BrPA from LA is illustrated in Scheme 3. Note that the zwitterion serves as HBr carrier and its chemical structure remains unchanged over the course of the reaction. Therefore, successful reloading and reuse of the salt over several bromination cycles is expected and will be demonstrated in this paper.



Scheme 3: LA bromination cycle using tailor-made zwitterionic HBr carrier.

Screening of HBr -carrying zwitterions

To start our experimental work with HBr -loaded zwitterions as LA bromination agents, we tested different zwitterion structures to identify structural requirements for this particular application (see Table 1).

Table 1: LA bromination using different brominating agents: comparison of aqueous HBr (48 wt%) and different SO₃H-functionalized bromide ionic liquids.

Entry	HBr source	X _{LA} / % ^[a]	Y _{2-BrPA} / % ^[a]	S _{2-BrPA} / % ^[a]
1	HBr(aq)	40	20	50
2	[MIMBS]Br	48	48	> 99
3	[PyrBS]Br	69	54	78
4	[PBu ₃ BS]Br	oligomerization	0	0

Reaction Conditions: 0.05 mol lactide, 0.30 mol HBr source, 120 °C, 5 h, ambient pressure; [MIMBS]Br = 1-(4-butane sulfonic acid)-3-methyl imidazolium bromide; [PyrBS]Br = 1-(4-butanefulfonic acid) pyridinium bromide; [PBu₃BS]Br = Tri-n-butyl-(4-butanefulfonic acid) phosphonium bromide; [a] conversion, yield and selectivity determined by ¹H NMR as $X_{LA} = \frac{n_{r,0} - n_{r,t}}{n_{r,0}}$,

$$Y_{2-BrPA} = \frac{n_p - n_{p,0}}{n_{r,0}} \cdot \frac{|v_r|}{v_p} \text{ and } S_{2-BrPA} = \frac{n_p - n_{p,0}}{n_{r,0} - n_{r,t}} \cdot \frac{|v_r|}{v_p} = \frac{Y_p}{X_r}, \text{ respectively; } n_r = \text{moles of reactant; } n_p = \text{moles of product.}$$

The zwitterions that contain nitrogen (entries 2, 3) were active in the bromination of LA towards 2-BrPA. In contrast to HBr_(aq), these ionic liquid HBr carriers proved to be highly selective to 2-BrPA. The highest S_{2-BrPA} in this first screening was achieved with [MIMBS]Br. With this system, no by-products were observed in ¹H NMR and the mass balance could be entirely closed. In contrast, phosphonium-based ionic liquids did not show any activity. [PBu₃BS]Br was inactive in the bromination under standard conditions (120 °C) and only lactic acid oligomers were observed after 5 h in ¹H NMR. At bromination temperatures above 120 °C, all systems showed an increasing tendency to promote substrate oligomerization / polymerization, as well as decarbonylation to acetaldehyde and CO.

To further reveal influencing effects on the selectivity and yield of the 2-BrPA synthesis, zwitterion-derived bromide salts of different lipophilicity and acidity were investigated. The respective results are shown in Figure 1.

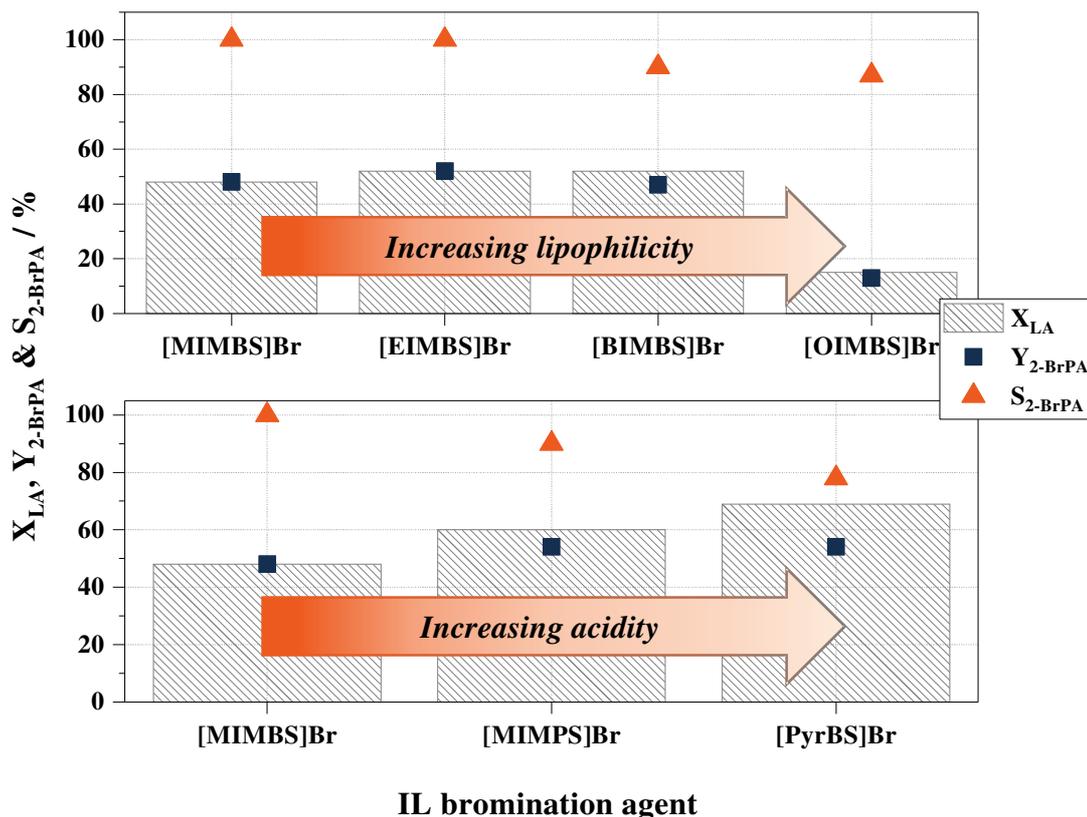


Figure 1: Influence of cation lipophilicity (top) and acidity (bottom) of the zwitterion-based bromide IL on 2-BrPA synthesis; conditions: 12.5 mmol lactide, 75 mmol IL, 90 mol% HBr loading grade of IL, water content of ~ 3 wt%, 5 h, 120°C; [EIMBS]Br= 1-(4-butane sulfonic acid)-3-ethyl imidazolium bromide, [BIMBS]Br= 1-(4-butane sulfonic acid)-3-butyl imidazolium bromide, [OIMBS]Br= 1-(4-butane sulfonic acid)-3-octyl imidazolium bromide, [MIMPS]Br= 1-(3-propane sulfonic acid)-3-methyl imidazolium bromide.

Increasing lipophilicity in the bromide ionic liquid is easily realized by extending the alkyl chain attached to the imidazolium cation (Figure 1, top part). While replacing the methyl group in the [MIMBS] cation by an ethyl group does not influence the bromination activity significantly, the use of [BIMBS]Br already shows a clearly decreased Y_{2-BrPA} and S_{2-BrPA} . With the very lipophilic [OIMBS]Br as brominating agent for LA, the activity drops drastically. From these results we conclude that a decreased polarity of the reaction medium slows the rate of the bromination reaction, probably due to less efficient charge stabilization during the course of the bromination reaction.

The bottom part of Figure 1 shows the influence of the acidity of the zwitterion-based bromide IL on the bromination selectivity and yield. It is known from the literature^[24] that the IL acidity increases in the following order: [MIMBS]Br < [MIMPS]Br < [PyrBS]Br.^[27] We observed a decreasing S_{2-BrPA} as acidity increased from the mildly acidic [MIMBS]Br to the stronger acids [MIMPS]Br and [PyrBS]Br (see Figure 1). This confirmed our assumption that too high acidity is detrimental to S_{2-BrPA} as substrate decarbonylation and self-oligomerization are favored in strongly acidic media.

The following set of experiments has been carried out using the IL [MIMBS]Br. This selection was made due to the very attractive performance of this IL in the screening experiments (see Table 1 and Figure 1), but also based on economic considerations. MIMBS is easily produced in large quantities from the reaction of two commercial compounds: 1-methyl imidazole and 1,4-butane sultone.

LA bromination using [MIMBS]Br - temperature variation

In a first set of experiments, we investigated the influence of the reaction temperature (T_r) on the selectivity of the LA bromination with [MIMBS]Br. The results are shown in Figure 2. Starting at our initial screening temperature of 120°C with a substrate to IL ratio of 1:3, an IL residual water content of < 1.5 wt%, and HBr loading of 75 mol%, we achieved $Y_{2\text{-BrPA}}$ of 35% and $S_{2\text{-BrPA}}$ of approximately 100% within 5 h. No by-products were observed by ^1H NMR and the mass balance was closed. Working at temperatures lower than 120°C led to a reduced LA conversion (X_{LA}), due to a reduced reaction rate. After LA bromination in [MIMBS]Br 100°C, we observed $Y_{2\text{-BrPA}}$ of only 9%. Interestingly, an increase of T_r to 140°C was not accompanied by a substantial additional increase in $Y_{2\text{-BrPA}}$ (37%). Instead, decarbonylation of LA was observed at 140°C leading to a decrease in $S_{2\text{-BrPA}}$. Moreover, the formation of 3-bromopropionic acid (3-BrPA) was observed from an emerging isomerization activity of the system. Our studies indicate that the so-formed 3-BrPA originates from a two-step isomerization process including AA formation from 2-BrPA and subsequent addition of HBr to AA to form 3-BrPA. Note that addition of HBr to AA under the applied reaction conditions forms highly selectively 3-BrPA. Moreover, heating of 2-BrPA in bromide salts in the absence of HBr forms AA as major compound as reported by Terrade et al.^[11]. Thus, the combined yield of brominated LA species $Y_{\text{X-BrPA}}$ ($Y_{2\text{-BrPA}} + Y_{3\text{-BrPA}}$) after 5 h reaction at 140°C increased to 49%, whereas the overall selectivity $S_{\text{X-BrPA}}$ decreased to 82%.

From our experiments we conclude that 120°C is the optimum T_r for the selective synthesis of 2-BrPA from LA in [MIMBS]Br. At this temperature, all side and consecutive reactions are suppressed to a very large extent and still acceptable reaction rates can be realized.

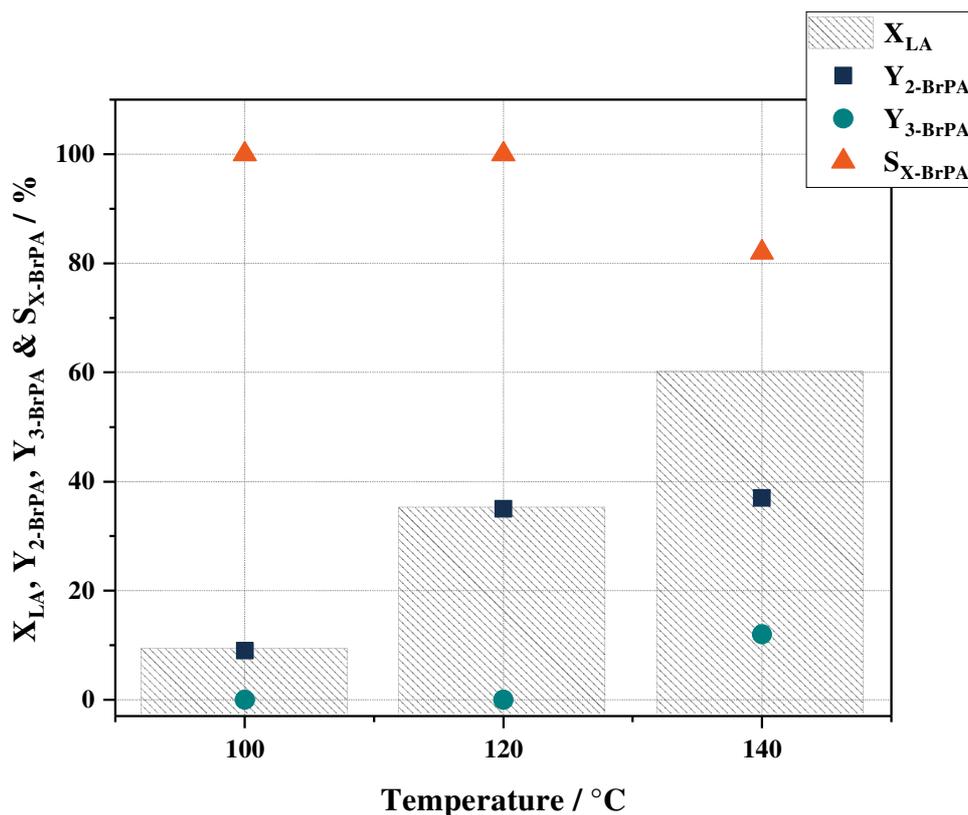


Figure 2: Temperature variation in the 2-BrPA synthesis from lactide using [MIMBS]Br as bromination agent; conditions: 12.5 mmol lactide, 75 mmol IL, 75 mol% HBr loading grade of IL, water content of < 1.5 wt%, 5 h.

LA bromination using [MIMBS]Br - molar ratio variation

In a second set of experiments, we investigated the influence of the molar ratio LA:IL on the outcome of the lactide bromination reaction (see Figure 3). As the ionic liquid reaction matrix was prepared with low initial water content, we assumed that an increasing amount of bromide IL should allow higher yields in 2-BrPA due to a more favorable position of the bromination/hydrolysis equilibrium. Consequently, we tested LA:IL ratios from 1:1 to 1:6 to confirm this expectation (see Figure 3). Indeed, we found increased Y_{2-BrPA} when the LA:IL molar ratio increased from 1:1 (29%) to 1:3 (48%). This increase in yield goes hand in hand with an increase in selectivity to 2-BrPA as substrate decarbonylation and self-oligomerization are effectively suppressed at the 1:3 ratio. However, no further improvement in Y_{2-BrPA} was observed when the LA:IL molar ratio was 1:6. Hence, a LA:IL molar ratio of 1:3 was found ideal for the bromination of lactide with [MIMBS]Br and is used in the following investigations. The decreased S_{2-BrPA} in the bromination experiment with an LA:IL ratio of 1:1 is assumed to result from non-hydrolyzed substrate (lactide) and comparably high substrate concentration. The low amount of water in the reaction medium in this experiment is insufficient for complete lactide hydrolysis and the remaining intermediate may lead to additional bromination and oligomerization by-products.

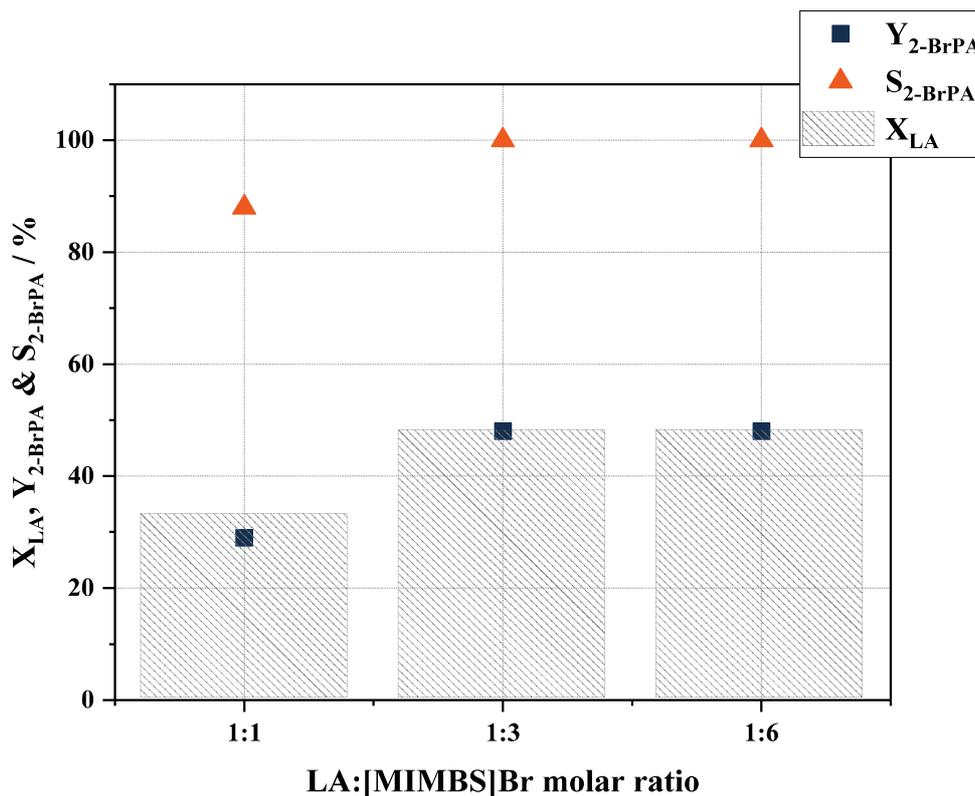


Figure 3: Concentration-dependent 2-BrPA synthesis with [MIMBS]Br; conditions: X mmol lactide, 75 mmol IL, ~ 90 mol% HBr loading grade of IL, water content of ~ 3 wt%, 5 h, 120°C.

Influence of water

The following experiments aim to shed more light on the role of water in the lactide bromination using [MIMBS]Br. In all experiments HBr was added as 48 wt% aqueous solution to the zwitterion followed by removal of water *via* azeotropic distillation (see Experimental Section for details) to defined water and HBr contents (see below).

After this procedure, the residual water content in the IL was monitored by *Karl-Fischer* titration. Moreover, acid-base titration of the removed water was carried out to determine the loss of HBr from the IL during water evaporation (see Experimental Section for details).

To study the influence of water more systematically, two different sets of experiments were performed: First, we prepared four samples of pre-dried [MIMBS]Br (75 mmol MIMBS, HBr loading grade: 75 mol%, ~3 wt% initial water content) and added varying amounts of additional H₂O (0.5 to 4.0 g). The results of these experiments are shown in Figure 4 (top). They clearly confirm that the presence of increasing amounts of H₂O negatively influences the bromination reaction. The more H₂O added, the lower the Y_{2-BrPA} after 5 h of reaction time was. An addition of 4 g (17.1 wt%) of H₂O, for instance, led to a significant drop of Y_{2-BrPA} to 14%, compared to Y_{2-BrPA} of 37% obtained by a water addition of only 0.5 g (3.8 wt%). In all of these experiments, an exceptional S_{2-BrPA} could be realized with no detectable

formation of by-products. Therefore, the presence of large amounts of water does not affect the selectivity towards 2-BrPA.

In the second set of experiments, we varied the drying times of the initial HBr-zwitterion solution to adjust the residual water content of the IL. The residual water content of the brominating reagent was monitored by the amount of trapped water in the *Dean-Stark* apparatus and the subsequent *Karl-Fischer* titration of the prepared ILs. The results of the LA bromination with [MIMBS]Br of different H₂O content produced by this loading method are shown in Figure 4 (bottom). In contrast to the results from the first set of experiments, no significant decrease of Y_{2-BrPA} was observed, although the residual water content tripled along this series. It is noteworthy that the ILs used in these experiments had a much higher HBr-loading grade of approximately 90 mol% (determined *via* acid-base titration of collected water) resulting from shortened drying times. From the results, we conclude that the HBr loading of the zwitterion has a dominating influence on the resulting Y_{2-BrPA} over the residual water content of the reaction matrix. Hence, to obtain an optimum brominating reagent for LA, the water content of [MIMBS]Br should be as low as possible to overcome the equilibrium-limiting influence. High loading grade of HBr on the zwitterion is even more important as the detrimental effect of water is much less pronounced for systems with high HBr concentrations.

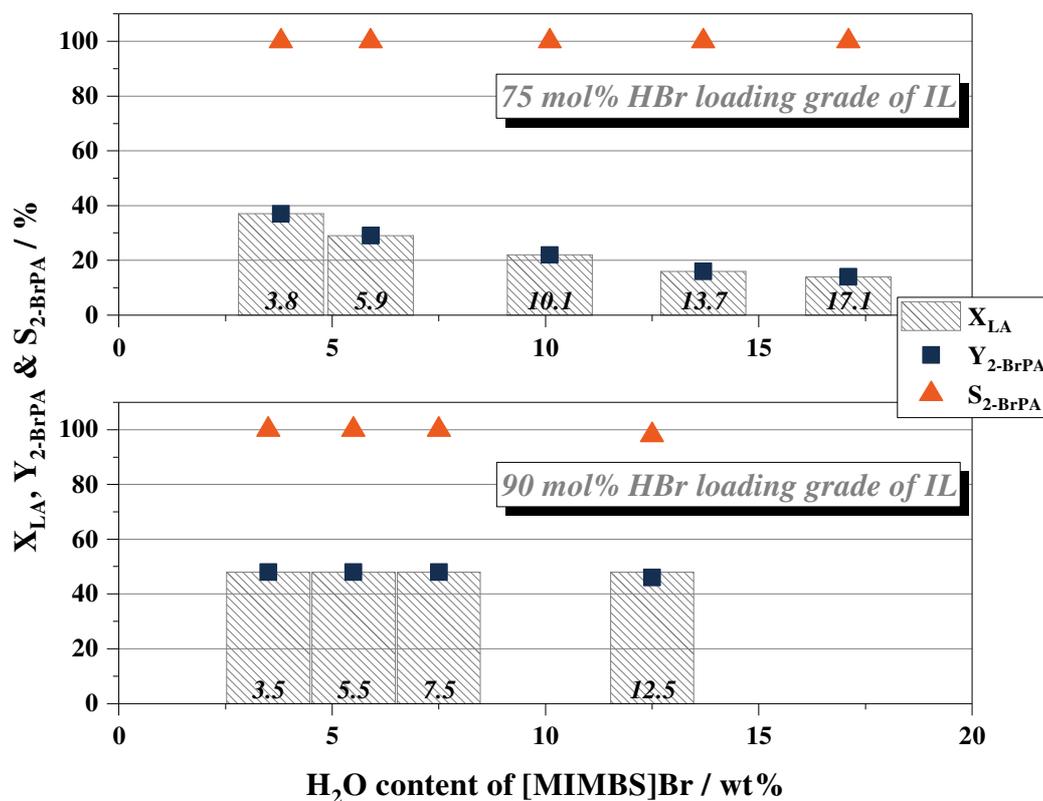


Figure 4: Influence of water content on 2-BrPA synthesis with [MIMBS]Br. Varying amounts of H₂O added prior to bromination after complete drying procedure (top) and varied residual H₂O content by incomplete drying procedure (bottom). conditions: 12.5 mmol lactide, 75 mmol IL, 5 h, 120°C.

Then, we attempted to increase the HBr loading to 100 mol% while keeping the water content of the system to a minimum. In the optimized HBr loading procedure, the MIMBS zwitterion was loaded with $\text{HBr}_{(\text{aq})}$ and subsequently dried at 100°C for 16 h to a residual water content below 1.5 wt%. The resulting HBr loading grade was determined *via* acid-base titration. HBr loss during the entire drying procedure corresponded to 24 mol% of the added HBr. Compensation of this loss was realized by adding again HBr in the form of its aqueous solution. The resulting IL contained 7.5 wt% of water and a formal HBr loading of 100 mol% (every sulfonic acid group protonated by HBr). By adding more aqueous HBr to the dried system, HBr loadings of 133 mol% were realized resulting in a water content of 14 wt% in this particular case. The results obtained with the [MIMBS]Br with different degrees of HBr loading and water have been compared under standard reaction conditions (120°C , 5h) and the corresponding results are shown in Figure 5.

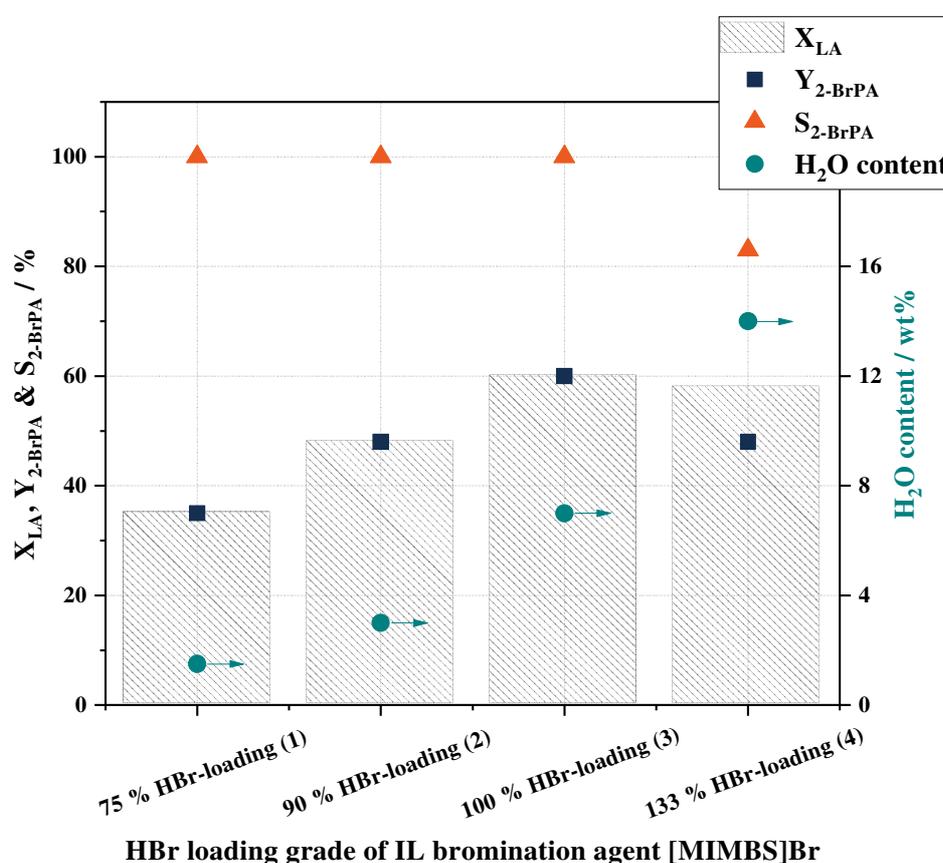


Figure 5: Influence of HBr loading grade and water content on 2-BrPA synthesis with [MIMBS]Br. conditions: 12.5 mmol lactide, 75 mmol IL, 5 h, 120°C . IL loading grade varied by preparation method (1, 2) and addition of $\text{HBr}_{(\text{aq})}$ after drying procedure (3, 4).

Increasing the HBr loading grade from 75 (Figure 5, entry 1) to 90 mol% (entry 2) led to an increase of $Y_{2\text{-BrPA}}$ from 35 to 48% despite the higher H_2O content of the higher-loaded reaction matrix. The fully-loaded IL (entry 3) achieved an even higher $Y_{2\text{-BrPA}}$ of 60% with a $S_{2\text{-BrPA}}$ of approximately 100%. No side-products were observed by $^1\text{H-NMR}$ spectroscopy and the mass balance was closed. However, over-saturation of [MIMBS]Br (entry 4) did not result in higher 2-BrPA yield and significant lactide

decarbonylation to acetaldehyde and CO was observed. This observation is attributed the fraction of “free HBr” (resulting from over-saturation of the zwitterion), increasing the acidity of the reaction medium and therefore decreasing $S_{2\text{-BrPA}}$.

Influence of reaction time

As the next step, we were interested to optimize the reaction time for the lactide bromination reaction. So far, all experiments were conducted for 5 h. For the time variation experiments, fully loaded [MIMBS]Br (100 mol% HBr loading, 7.5 wt% water) was used at 120°C with a molar ratio of LA:IL of 1:3. The results are shown in Figure 6.

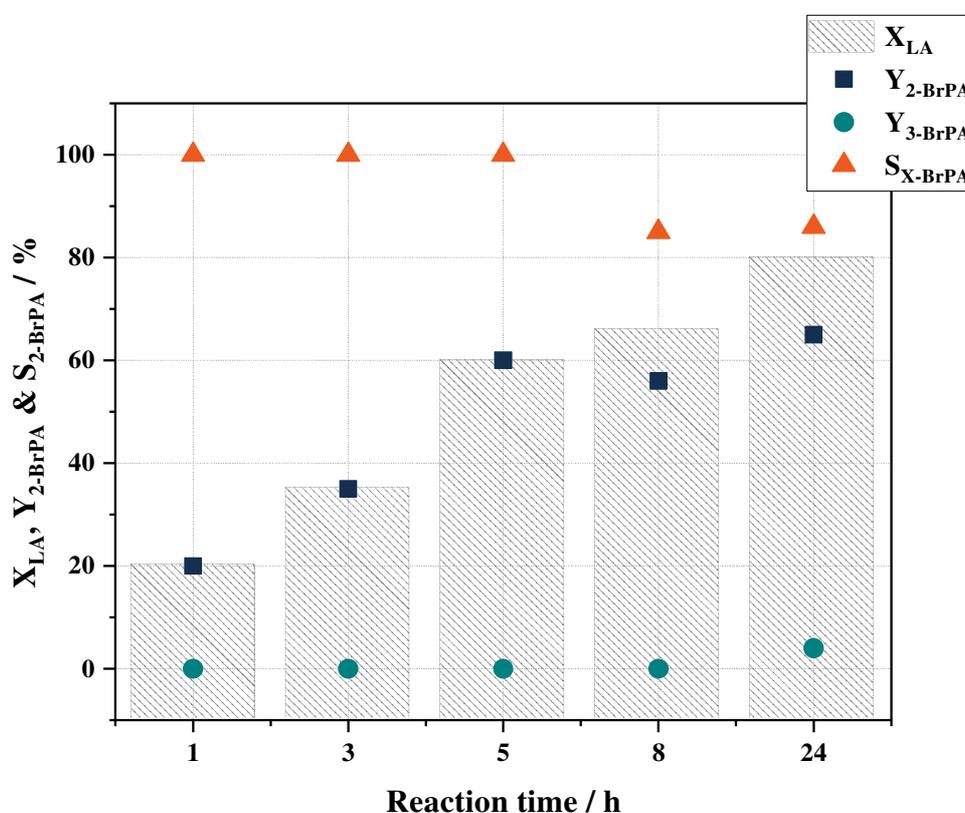


Figure 6: Time-dependent 2-BrPA synthesis with [MIMBS]Br Five independent bromination experiments with different reaction times. conditions: 12.5 mmol lactide, 75 mmol IL, full HBr loading grade of IL by compensating HBr lost during drying procedure, IL water content of 7.5 wt%, 120°C.

Our results indicate that reaction times longer than 5 h do not significantly increase the 2-BrPA yield. Instead, lactide conversion increases only slightly at prolonged reaction time combined with an increasing amount of side products formed. Interestingly, after 24 h reaction time also some 3-BrPA is found in the reaction solution (3%). This indicates that over long reaction times some of the 2-BrPA product forms AA by dehydrobromination followed by hydrobromination to 3-BrPA even at the mild reaction temperatures of 120°C.

2-BrPA isolation from aqueous IL phase via liquid-liquid extraction (LLE)

All experiments so far indicated that the 2-BrPA yield in the [MIMBS]Br reaction system is limited to around 60% but excellent selectivity could be achieved. A logic concept to drive the reaction to full conversion of the lactide substrate and 100% 2-BrPA yield was therefore to isolate the 2-BrPA formed after 5 h from the reaction mixture, regenerate the IL with fresh HBr, and convert the residual lactide from the first run.

For isolating 2-BrPA from the reaction mixture, liquid-liquid extraction (LLE) was chosen. *In-situ* LLE was examined first but led to a decrease in S_{2-BrPA} . Moreover, the realized partition coefficients K_{2-BrPA} were very low. Therefore, we investigated *ex-situ* LLE to isolate the formed 2-BrPA from the IL-containing reaction matrix. To ensure a stable liquid-liquid biphasic system for the extraction experiment, the IL reaction matrix was quenched with water after the bromination experiment to form an aqueous IL-containing phase. The added water stayed in the IL phase and was subsequently removed *via* azeotropic distillation (see Experimental Section). In the screening experiments for the extraction of 2-BrPA from the aqueous IL phase, various organic solvents were tested. The results are shown in Table 2.

Table 2: Results of *ex-situ* LLE solvent screening*.

Organic solvent	K_{2-BrPA}	T_b of extractor at 1 atm. / °C
toluene	0.21	111
chloro benzene	0.23	132
bromo benzene	0.17	156
diphenyl ether	0.15	258
chloroform	1.18	61
dibutyl ether (DBE)	1.82	141
1-heptanol	28.1	175

*Extraction conditions: 1 mL of quenched product solution, 1 mL of organic solvent, 24 h, room temperature, ambient pressure; T_b = boiling temperature; see Supporting Information for details on *ex-situ* LLE solvent screening.

The determined partition coefficients of 2-BrPA were in the range of 0.15 to 28.1, depending on the nature of the organic solvent. Whereas aromatics and aryl halides had low extraction ability for 2-BrPA, chloroform (1.18) and dibutyl ether (1.82) showed reasonable K_{2-BrPA} and can therefore be used for product isolation. 1-heptanol, however, showed by far the highest K_{2-BrPA} (28.1) of all tested extracting agents. However, for this solvent, additional LA was detected in the extraction phase (K_{LA} of 3.26) resulting in a selectivity of 8.62 in favor of 2-BrPA extraction. The other investigated extractors displayed high selectivity towards 2-BrPA, with no LA detectable in the 1H NMR spectra of the organic layer (details on 1H NMR measurements see Experimental Section). Hence, 1-heptanol can be used not

only for product and substrate isolation, but also for possible clean-up procedures of the IL reaction matrix after the bromination experiment.

Recycling of the zwitterionic reaction matrix

Finally, we investigated the recycling of the zwitterionic reaction matrix under optimized conditions. A detailed overview of the recycling procedure is given in the Experimental Section. In this recycling study, we isolated the formed product, 2-BrPA, after the bromination experiment using the two most attractive extraction solvents from our comparative study (see Table 2), DBE and 1-heptanol. As can be seen from Figure 7, the isolated amount of 2-BrPA ($n_{2\text{-BrPA}}$) is constant over four bromination cycles using 1-heptanol for product isolation ($n_{2\text{-BrPA}}$ is within the error of the standard experiment, see Supporting Information), indicating that HBr-reloaded zwitterionic-based molten salts maintain good activity during recycling. The same very encouraging recycling behavior was found for DBE as an extracting agent. Here, three recycling procedures were demonstrated. Note that in both recycling series, a drop of $Y_{2\text{-BrPA}}$ was observed with increasing number of bromination experiments, due to incomplete substrate (LA) extraction from the IL. Non-extracted LA was included into the calculation of $Y_{2\text{-BrPA}}$ of the subsequent experiment. This led to a formally decreasing $Y_{2\text{-BrPA}}$ with increasing number of bromination cycles. However, the constant, isolated amount (moles) of 2-BrPA in the organic layer clearly showed the recyclability of the brominating agent and reaction matrix over the performed cycles without any significant loss in HBr loading capacity.

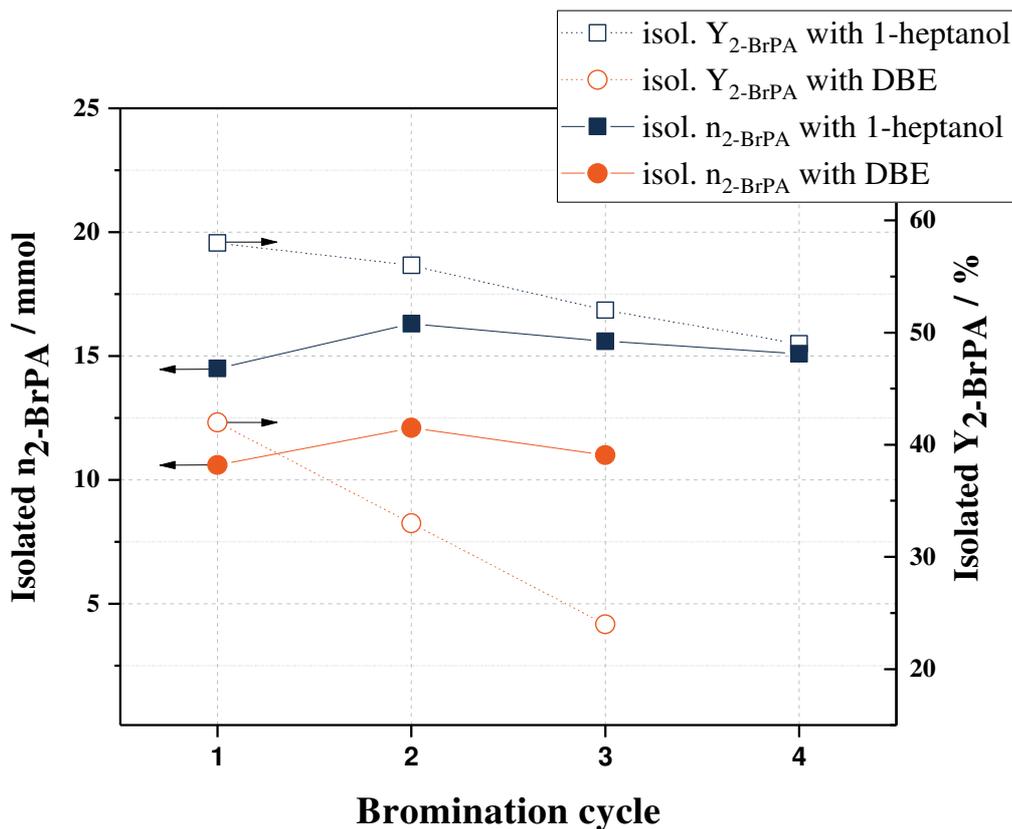


Figure 7: The effect of recycled [MIMBS]Br with 1-heptanol and DBE on the isolated n₂-BrPA and Y₂-BrPA of bromination of LA to 2-BrPA.

Conclusions

In summary, we developed a novel method for the synthesis of 2-BrPA starting from renewable lactide using SO₃H-functionalized bromide ILs. In our proposed concept, a zwitterionic-based molten salt serves as water-free HBr carrier and acidity buffer. When the zwitterionic-based molten salt is loaded with HBr, the formed ionic liquid has been shown to act as a selective and efficient brominating agent and reaction matrix (solvent, proton source, and buffer) for the bromination of LA to 2-BrPA. Especially, imidazole-based ILs showed exceptional selectivity in the synthesis of 2-BrPA from lactide. The best results were obtained with [MIMBS]Br and [EIMBS]Br reaching 60% yield to 2-BrPA and 100% selectivity. This finding is in sharp contrast to the same reaction performed in aqueous HBr (48 wt% HBr) where decarbonylation and self-oligomerization dominated and a maximum yield of only 20% could be achieved under otherwise comparable reaction conditions (120°C, 5 h, and ambient pressure). Moreover, product and substrate isolation, as well as brominating agent recycling, have successfully been demonstrated. Given the unique ability to selectively produce 2-BrPA from bio-renewable feedstock, we expect this route to contribute substantially to the field of regenerative production of platform chemicals. Efforts are in progress to apply this new methodology to the synthesis of bio-AA. Detailed studies on this novel technology for a liquid-phase dehydration of lactic acid to bio-AA *via* brominated intermediates are ongoing in our laboratories and will be reported elsewhere. We

anticipate that the bromination methodology described in this paper will also be transferable to the selective bromination of other hydroxyl functionalized, complex substrates.

Experimental Section

All used chemicals were purchased from commercial suppliers and used without further purification. Bio-based feedstock lactide, namely PURALACT® (L-lactide, polymer grade), was provided by Corbion.

Preparation of zwitterions

All zwitterions were prepared *via* altered synthetic routes according to Yoshizawa et al.^[28] and Cole et al.^[29]. For the preparation of the zwitterion, equimolar amounts of the respective nucleophile (imidazole, pyridine, phosphine) and the respective sultone (1,4-butanedisulfone or 1,3-propanedisulfone) were dissolved in acetonitrile and refluxed for 48 h. The product precipitated over the course of this reaction. After cooling to room temperature, the residue was thoroughly washed and dried in vacuum. Products were analyzed *via* ¹H and ¹³C NMR spectroscopy. All products were obtained as white powders in very good yield and excellent purity. Details can be found in the Supporting Information.

Loading of zwitterions with HBr

The ionic liquid bromination medium was prepared from the zwitterion by first mixing equimolar amounts of the latter (75 mmol) with 48 wt% hydrobromic acid (HBr_(aq), 75 mmol) in a 100 mL three-necked glass reactor. To facilitate stirring and ensure homogeneity of the reaction mixture, two additional milliliters of water were added. After vigorous stirring for 15 minutes, a clear and colorless solution was obtained. 50 mL of cyclohexane were added at room temperature and atmospheric conditions. The biphasic reaction mixture was heated to a temperature of 69.8°C under continuous stirring with a magnetic stirring bar at a speed of 600 rpm for 16 to 24 h. The protic and HBr-loaded ionic liquid was isolated by removing the water using a Dean-Stark-apparatus and finally decanting the cyclohexane phase off after the reactor was cooled down to room temperature. All active HBr-loaded ionic liquids were obtained as highly viscous and hygroscopic oils.

Characterization of HBr-loaded ionic liquids

The HBr-loading of the ionic liquid was monitored by acid-base titration of the HBr-enriched water that was removed during the drying procedure. Aqueous NaOH solution (1 M) was dropwise added until the acidic solution was neutralized. This was followed by color-change of the previously added ethanolic phenolphthalein indicator solution (0.1 mL). Assuming that no HBr is lost over the gas-phase, acid-base titration of the trapped water allows to determine the HBr content of the prepared ionic liquid according to the following equation:

$$n_{\text{loaded HBr}} = n_{0 \text{ HBr}} - n_{\text{titrated NaOH}}$$

A reference experiment of direct HBr determination by acid-base titration of the solved and loaded IL resulted in a fully closed HBr balance ($n_{0 \text{ HBr}} = n_{\text{loaded HBr}} + n_{\text{titrated NaOH}}$) and therefore confirmed the developed method.

The residual water content of the IL was analyzed *via* Karl-Fischer titration (Metrohm 756 KF Coulometer, the single-component solution used for the analysis was apura® CombiCoulomat fritless Karl Fischer reagent for coulometric water determination, Merck) in dry methanol. Standard water contents determined were ≤ 3 wt%.

Bromination reactions with HBr-loaded ionic liquids

The bromination of lactide with zwitterion-based bromide ionic liquids was carried out in a 100 mL three-necked glass reactor. Lactide (L, L- lactide, polymer grade, Corbion Purac Co., Lenexa, KS) was added to the HBr-loaded zwitterion in the desired molar ratio. The amount of HBr was readjusted by addition of aqueous hydrobromic acid (HBr, 48 wt%, Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany, catalog # 244260), if necessary. The activated reaction mixture was heated to the desired reaction temperature under continuous stirring with a mechanical overhead stirrer at a speed of 600 rpm. The reaction mixture was refluxed and all gaseous products were alternatively trapped in a gas sampling bag for qualitative analysis or collected in a hydrostatic column for gas quantification. After an overall process time of 1 to 24 h, the reaction mixture was quenched with methanol (CH₃OH, 99.8%, anhydrous, Sigma Aldrich, Chemie GmbH, Taufkirchen, Germany; catalog # 322415) and the reaction mixture was analyzed *via* off-line ¹H NMR for quantification of its composition.

Recycling of zwitterions

After completion of the bromination reaction, the reaction mixture was quenched with 10 mL water instead of the methanol quench mentioned above. When cooled to room temperature, the quenched reaction medium was extracted (3x20 mL) with an organic solvent to remove the product from the aqueous phase. The combined organic phases as well as the aqueous phase were quantitatively analyzed by ¹H NMR spectroscopy to give an isolated product yield ($Y_{AA, \text{isolated}}$) and to determine the amount of non-isolated C₃ compounds. Finally, the aqueous IL phase was reused for another HBr loading experiment followed by a new bromination cycle.

Analysis, quantification and calculations

All qualitative and quantitative NMR spectra were recorded on a JEOL ECX 400 MHz instrument with a sample temperature of approximately 20°C. Chemical shifts were reported relative to the peak of Si(CH₃)₄ using ¹H-(residual) chemical shifts of the deuterated solvent as a secondary standard and are reported in ppm. ¹H scans were conducted with an excitation frequency of 399.72 MHz and 8 scans. ¹³C NMR spectra were recorded with an excitation frequency of 100.51 MHz and 250 scans.

Conversion (X), yield (Y) and selectivity (S) of all performed experiments were determined *via* the integrals of the corresponding peaks in the ^1H NMR spectrum, using the following equations (with r = reactant, p = product, ν = stoichiometric coefficient).

$$X_r = \frac{n_{r,0} - n_{r,t}}{n_{r,0}}$$

$$Y_p = \frac{n_p - n_{p,0}}{n_{r,0}} \cdot \frac{|\nu_r|}{\nu_p}$$

$$S_p = \frac{n_p - n_{p,0}}{n_{r,0} - n_{r,t}} \cdot \frac{|\nu_r|}{\nu_p} = \frac{Y_p}{X_r}$$

The concentration ratio of a species i in the organic phase and the aqueous phase correspond to the partition coefficient K_i . The concentration c_i can be obtained from the molar amount n_i and the volume of the respective phase, whereby n_i was obtained from ^1H NMR spectroscopy using an internal standard (IS) integral for quantification purpose. The selectivity of the extraction agent can be obtained by the ratio of the respective partition coefficients. The following equations were used to determine the partition coefficient of the substrate LA (K_{LA}), the product 2-BrPA (K_{2-BrPA}), and the extraction selectivity towards 2-BrPA ($S_{LLE,2-BrPA}$).

$$K_{2-BrPA} = \frac{c_{2-BrPA(org)}}{c_{2-BrPA(aq)}} \quad K_{LA} = \frac{c_{LA(org)}}{c_{LA(aq)}}$$

$$S_{LLE,2-BrPA} = \frac{K_{2-BrPA}}{K_{LA}}$$

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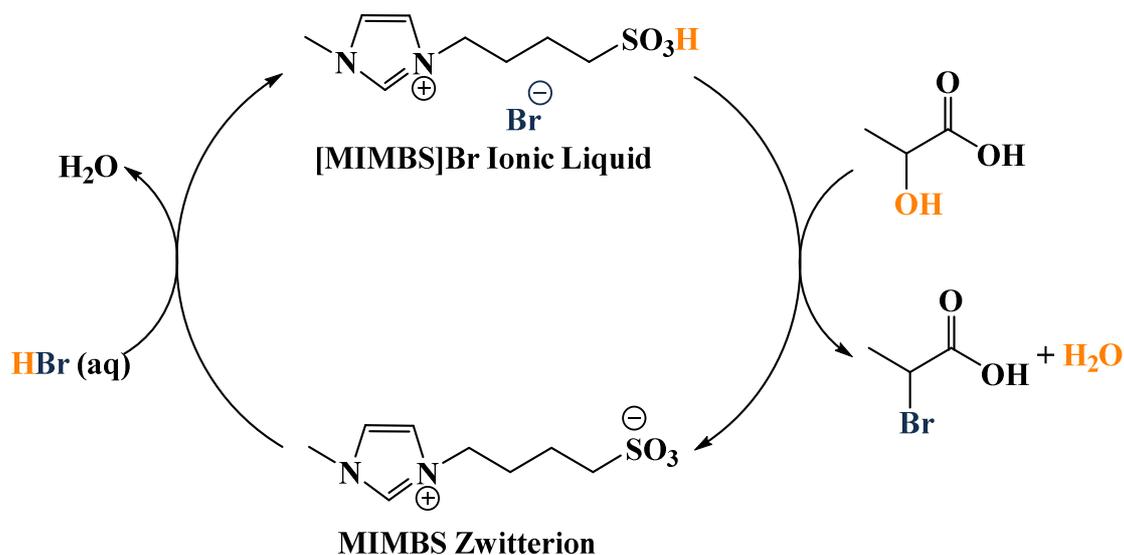
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Graphic Abstract



LA bromination cycle using tailor-made zwitterionic HBr carrier.

A convenient and efficient way of synthesizing 2-bromopropionic acid (2-BrPA) from lactide using zwitterionic HBr carriers is presented. The reaction is performed in ionic liquids (ILs) obtained from HBr addition to ammonium-based zwitterions, serving as solvent and bromination agent. The character of the IL reaction matrix enables 2-BrPA synthesis with excellent selectivity. Given the unique ability to selectively produce 2-BrPA from bio-renewable feedstock, we expect this route to contribute substantially to the field of regenerative production of platform chemicals.