Sistemes basats en sals d'imidazoli: Plataforma pel desenvolupament de compostos d'interès químic i farmacèutic

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SISTEMES BASATS EN SALS D'IMIDAZOLI: PLATAFORMA PEL DESENVOLUPAMENT DE COMPOSTOS D'INTERÈS QUÍMIC I FARMACÈUTIC

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6. ANNEX

6. 1. PUBLICACIONS (CAPÍTOLS 2 i 3.1)

- **Imidazolium ionic liquids: A simple anion exchange protocol.**
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Imidazolium ionic liquids: A simple anion exchange protocol†‡

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An efficient and simple protocol was developed to obtain quantitative iodide or bromide exchange for a broad range of anions in imidazolium ionic liquids. Selected anions were loaded in an anion exchange resin using two different procedures and were then used to provide a pure convenient ion pair.

Over the last few years, imidazolium-based frameworks have been developed as room-temperature ionic liquids (RTILs)[2] and there have been advances in anion recognition chemistry[1,3] as well as in N-heterocyclic carbenes (NHCs)[4,5] and their applications. Designed as greener solvents, the room-temperature ionic liquids (RTILs) have been attracting increasing interest as a potential alternative to conventional volatile organic solvents.[2] They are composed of bulky organic cations and a variety of anions whose characteristics can be tailored and tuned by a suitable choice of the cation/anion combination. The basicity, geometry and polarizability of anions are crucial not only for ion pair-formation but also for their role as technicophores, because they exhibit a high potential for tuning technological properties (*e.g.* solubility, viscosity, *etc.*).[6] Moreover, the anion as a toxicophore/ecotoxicophore of an ionic liquid can influence biological effects.[7] On the other hand, chiral anions such as (S)-lactate[8] or (S)-canphorsulfonate[9] in [bmim] salt have been used to induce diastereoselectivity.[10]

Ionic liquids have also recently attracted interest as benign solvent systems for the synthesis of nanomaterials[11] and they are emerging as alternative liquid templates for the generation of a plethora of size- and shape-controlled nanostructures. The morphologies of the metal products are more sensitive to the nature of the anions compared to the cations of the RTILs.[11c,d]

Considering these facts, the possibility of being able to systematically vary the anion constitutes an important factor in reaching the goal of sustainable design of 'task specific ionic liquids'.

The most popular RTILs are the widely employed N,N′-dialkylimidazolium salts, even though they could be considered as non-innocent solvents[12] due to the acidity of C(2)-H. A typical preparation of these salts is the quaternization of N-alkylimidazole with haloalcanes followed by anion exchange.

Over the past few years an enormous variety of halide exchange reactions have been reported. Common methods are based on either double-displacement (treatment with metal or ammonium salts) or acid–base neutralization reactions, and the resulting halide-containing by-product salts are subsequently removed by extraction or precipitation followed by filtration.[2,13] However, the purity as well as the final yield of the process continues being a motive of interest for improvement. Acids remain the ideal source of the desired anions to minimize inorganic contamination. Since an anion exchange cannot be efficiently done with the imidazolium halide and an acid weaker than a hydrohalic acid, the route to a wider range of conjugate bases must pass through a different intermediate. Based on the acidity of the C(2)-H in the imidazolium unit,[14] Earle and Seddon[15] proposed the use of strong bases to provide the formation of NHCs, which are then reprotonated with acid and consequently could potentially incorporate a large number of anions. However, it is necessary to take care with this procedure, given the stability and reactivity of the carbene intermediate.

On the other hand, ion exchange resins have been employed as an efficient tool to perform the anion exchange and their application has been extended to a variety of chemical reactions. Our research group have long used anion exchange resins and described protocols to obtain imidazolium azolate inner salts[16] or to perform halide exchange to PF_6^- through the betaine[17a] or the OH^- salt[17b,c] using Amberlite (OH form).

In the field of ionic liquids, Amberlite (OH form) is used to exchange halides by OH^-, and then acid compounds are added to the solution obtained, the hydroxide being displaced by the new anion through an acid–base reaction. This procedure is useful whenever the intermediate hydroxide salt is stable. Thus, applying this protocol, Ohno and coworkers prepared bio-RTILs when organic acids or natural aminoacids were added to the solution.[18] However, to the best of our knowledge, there are only a few examples in the open literature describing the anion incorporation in the resin before the anion exchange is carried out in a RTIL. In this way, a strong base anion-exchange resin (OH form) was loaded with camphorate, acetate, mesylate, tosylate or lactate from the corresponding acid, and [OTs],[9a] [SO_4],[9b] [I][19a] or [Cl][19b] were substituted by the organic anion.

As a part of our ongoing research into imidazolium-based frameworks,[1] we herein report an efficient and practical procedure using anion-exchange resins to obtain ionic liquids based on imidazolium salts with the selected anion counterpart in quantitative yield. (see Fig. 1)

Seeking a more efficient means of halide removal, we decided to explore the use of an anion exchange resin (AER) conveniently loaded with the new desired anion to afford the expected ion pair.

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† Imidazolium-based frameworks. 21. Part 20: ref 1.

‡ Electronic supplementary information (ESI) available: Experimental procedures and spectral data. See DOI: 10.1039/b915743n

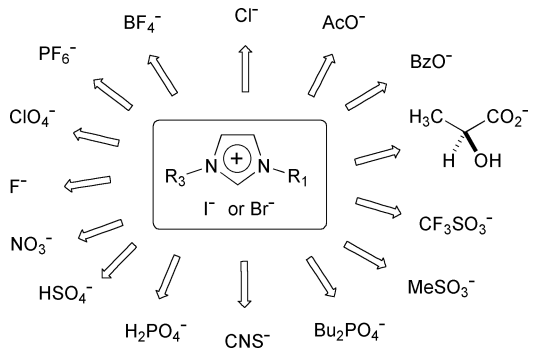

Fig. 1 Selected anions investigated to perform the halide exchange in imidazolium ionic liquids.

The initial targets of exchange were carboxylate anions, and [bmim][I] was used for carrying out the conversion. The strongly basic anion exchange resin Amberlist A-26 (OH form) was selected, given that it allows the use of aqueous mixtures and non-aqueous solvents, which facilitates the use of acids with low solubility in water. A packed column was treated with a carboxylic acid hydro-methanolic solution. The process involves the acid–base reaction with OH^-, resulting in the retention of the carboxylate anion in the resin and the displacement of the formed water together with the eluted solution (see Fig. 2).

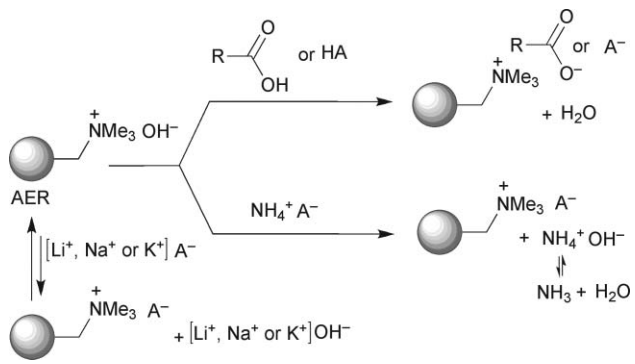

Fig. 2 Chemical processes involved when anion exchange resin OH^- form was treated with acids (organic or inorganic), ammonium salts, or alkaline salts.

A methanolic [bmim][I] solution was passed through a column packed with the A-26 ($R\text{-}CO_2^-$ form) and [bmim][AcO], [bmim][BzO] or [bmim][(*S*)-lactate] were quantitatively obtained after solvent elimination, confirmed by ^1H NMR. Remarkably, no evidence of NHC formation was observed, despite the basic media.

In order to expand the range of introducible counterions, the resin was charged with oxoanions derived from sulfonate ($MeSO_3^-$) or phosphate ($Bu_2PO_4^-$) together with inorganic anions such as Cl^-, NO_3^-, ClO_4^- or BF_4^- by treatment with the corresponding diluted acidic solutions. When the [bmim][I] solution was passed through the conveniently packed column, the exchange was carried out in quantitative form. The integration of the signal corresponding to the organic substituent in ^1H NMR showed the total exchange of I^- anion by $MeSO_3^-$ or $Bu_2PO_4^-$, whereas the C(2)-H chemical shift value in the imidazolium moiety indicated the substitution by inorganic anions.[20] Moreover, ESI(–)-MS experiments qualitatively confirmed that I^- was not present in the samples from the inorganic anion exchange,[21] according to the silver chromate test[19b] (< 20 ppm) (see ESI‡). This simple procedure allowed us to quickly and cleanly exchange the I^- anion, which was retained in the column, obtaining the pure new ion pair after the in vacuum solvent elimination. On the other hand, AER was recycled to the OH form, by treatment with a 10% NaOH aqueous solution, being available for re-use in another exchange process.

Encouraged by these results, our focus shifted toward the introduction of a new set of weakly basic anions. However, the treatment of the resin with strong acids can denaturalize the polymeric matrix by overheating during the loading, due to the high exothermic acid–base reaction. To circumvent this problem we developed a novel method to exchange hydroxide anions based on the use of ammonium salts, directly loading the anions by the reaction of the acidic cation with the basic OH^- of the resin. The aim of this procedure was to exchange OH^- for the new anion, which led to the formation of ammonium hydroxide. In aqueous solution most of this weak base remained dissociated in ammonia and water, so it did not displace the loaded anion (see Fig. 2).

The Amberlist A-26 (OH form) resin was treated with $AcONH_4$ or $ClNH_4$ aqueous solution in order to check that the loading had been effective. When the [bmim][I] solution was passed through the new charged resin, [bmim][AcO] or [bmim][Cl] were obtained in quantitative form, confirmed by comparison with the same ion pair obtained from the acid charged resin. These results confirm that the anion exchange resin can be conveniently loaded with the desired anion from the corresponding ammonium salt.

Likewise, following this procedure, $CF_3SO_3^-$ and $(CN)S^-$ anions as well as inorganic anions such as F^-, PF_6^-, $H_2PO_4^-$ or HSO_4^- were loaded in the AER (see Table 1). Complete exchange was achieved when [bmim][I] methanolic solution was passed through the column and, in all cases, ESI(–)-MS confirmed the nature of the new ion pair,[22] and the qualitative absence of the iodide anion. Although some anions (only AcO^-, Cl^- and PF_6^- were studied) could be loaded by both protocols, the use of acid was the best procedure for organic anions, and ammonium salts for inorganic anions.

On the other hand, we attempted to load the AER with the $(TfO)_2N^-$ or $MeSO_4^-$ from their commercially available Li^+ or K^+ salt, respectively. Neither of these two anions were exchanged in the resin (OH form),[23] which indicated that cations play an

Table 1 Anion source for loading Amberlist A-26[a]

Anion	Source	Anion	Source
AcO^-	AcOH, $NH_4^+AcO^-$	F^-	$NH_4^+F^-$
BzO^-	BzOH	Cl^-	$NH_4^+Cl^-$, HCl
(*S*)-Lactate$^-$	(*S*)-Lactic acid	PF_6^-	$NH_4^+PF_6^-$, HPF_6
$MeSO_3^-$	$MeSO_3H$	$H_2PO_4^-$	$NH_4^+H_2PO_4^-$
$Bu_2PO_4^-$	Bu_2PO_4H	HSO_4^-	$NH_4^+HSO_4^-$
BF_4^-	HBF_4	$CF_3SO_3^-$	$NH_4^+CF_3SO_3^-$
ClO_4^-	$HClO_4$	$(CN)S^-$	$NH_4^+(CN)S^-$
NO_3^-	HNO_3		

[a] A hydro-alcholic or methanolic acid solution or aqueous ammonium salt solution were used for the loading of selected anions in AER.

important role in successful AER anion loading. When the anion exchange took place within the resin, alkaline salts (LiOH or KOH) were formed. In contrast with ammonium hydroxide, the OH^- anion in these strong bases displaced the new anion, which reversed the process and returned the resin to the OH form (see Fig. 2).[24] This aspect was confirmed when we treated A-26 (OH form) with a NaCl solution and the Cl^- exchange did not take place, although it was successfully loaded with HCl or NH_4Cl (see Table 1).

Having examined the exchange of the iodide anion, the same process was explored from the bromide imidazolium salt. Thus, treatment of [bmim][Br] with the corresponding AER, conveniently loaded with the selected anion, led to the complete exchange of Br^-, as had occurred with the I^- anion.

Regarding other ionic liquids based on imidazolium salts, [bbim][I] and [bbim][Br] were examined as well as [mmim][I], and in all cases I^- or Br^- exchange was obtained. Exceptionally, treatment of [mmim][I] afforded a quantitative exchange, although in some instances the recovery of the new ion pair was only about 90–95%.

In all cases, the purity of the ionic liquids obtained was qualitatively determined using ^{1}H-NMR spectra, and/or ESI(–)-MS experiments, and the original halide was not observed. According to the silver chromate test, most analysis indicated the low halide contents (< 20 ppm). Further quantification of possible halide impurity was restricted by instrumental limitation.

In summary, we have developed an efficient, simple and practical procedure for the exchange of iodide or bromide for a variety of anions in imidazolium ionic liquids, using an anion exchange resin. The preparation of an AER conveniently loaded with a new selected anion by treatment with acid or ammonium salts not only offers an efficient tool to prepare the appropriate ion pair, including task-specific and chiral RTILs, but it is also recyclable and minimizes the formation of toxic by-products, with the corresponding environmental benefits. Our current efforts are being directed to broadening the protocol to an increased number of anions and ionic liquids, using non-aqueous media for the loading and exchange procedures.

Acknowledgements

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21 In some assays, the residual iodide anion was observed (< 5 %) but it was eliminated by a second treatment with the corresponding AER.
22 The results of fluoride anion exchange were compared with those obtained with [bmim][Br], which were able to be analyzed by High Performance Liquid Chromatography (HPLC) (see Electronic Supplementary Information).
23 In order to check that the loading had taken place, the anion exchange of [bmim][I] was performed in a conveniently packed column, and the eluted solution was analyzed.
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Imidazolium ionic liquids: A simple anion exchange protocol

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Supporting information

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General Information

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) spectrometer at 298 K. ^{1}H and ^{13}C chemical shifts were referenced with TMS as an internal reference.

Mass spectrometric analyses were performed on a LC/MSD-TOF (2006) mass spectrometer with a pumping system HPLC Agilent 1100 from Agilent Technologies at Serveis Científico-Tècnics of Universitat de Barcelona under the following experimental conditions: • Solvent: H_2O:CH_3CN (1:1, v/v) • Gas temperature: 300 ºC • Capillary voltage: 4 KV (positive) and 3.5 KV (negative) • Fragmentor: 75/175 V • Spray gas: N_2 pressure = 15 psi • Drying gas: N_2 flow: 7.0 $L \cdot min^{-1}$ • Flow rate: 200 $\mu L \cdot min^{-1}$.

HPLC was performed on a KONIK KNK 500-A chromatographer with automatic KONTRON AUTOSAMPLER 465 injector, and a WATERS IC-PAK ANIONS column that contains a polymetacrilate polymer with quaternary ammonium moiety. Eluent flow rate was 1 mL/min. Detection was carried out with WESCAN conductivity detector and UV KONTRON 332 detector. The aqueous samples (*ca* 50 ppm) were filtered (0.2 µm porous diameter) and organic components were separated by filtration through a C-18 column. The chromatograms were recorded, and the area under the curve (mV·min) against ppm was measured.

The pH was measured with *Crison micropH 2001*, using pH electrode for hydroalcoholic solutions.

Commercially available products: 1-butyl-1*H*-imidazole, 1-methyl-1*H*-imidazole, 1-iodobutane, 1-bromobutane, 1-iodomethane, ion exchanger resin Amberlyst A-26 (Aldrich®, OH^- form), glacial acetic acid, benzoic acid, (*S*)-lactic acid (85% solution in water), methanesulfonic acid, dibutylphosphoric acid, hydrochloric acid (37% in water), hexafluorophosphoric acid solution (65%, gravimetric in water), Tetrafuoroboric àcid (50 % in water), perchloric acid (70 % in water), nitric àcid (65 % in water)ammonium acetate, ammonium fluoride, ammonium chloride, ammonium hexafluorophosphate, ammonium phosphate monobasic, ammonium hydrogensulfate, ammonium thiocyanate and ammonium trifluoromethanesulfonate . All solvents were reagent grade and dried, if it is necessary, with molecular sieves. Methanol was distilled prior to use.

1-Buthyl-3-methylimidazolium iodide [bmim][I]

An oven-dried resealeable tube was back-filled with argon and charged with 1-butyl-1*H*-imidazole (0.95 g, 7.645 mmol) and iodomethane (3.42 g, 24.10 mmol) and the reaction mixture was stirred magnetically at 50 ºC for 24 h. After cooling the reaction mixture was evaporated to dryness, and the residue was washed with dry diethyl ether (3 x 25 mL) in a ultrasonic bath, obtaining the pure **[bmim][I]** as a colourless oil (2.00 g, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (t, *J* = 7.3 Hz, 3H), 1.34-1.46 (m, 2H), 1.87-1.97 (m, 2H), 4.12 (s, 3H), 4.33 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 1.8 Hz, 1H), 7.43 (t, *J* = 1.8 Hz, 1H), 10.13 (s, 1H).

1-Buthyl-3-methylimidazolium bromide [bmim][Br]

A solution of 1-methyl-1*H*-imidazole (2.415 g, 29.41 mmol) and 1-bromobutane (4.765 g, 35.038 mmol) in 50 mL of dry acetonitrile was stirred under reflux for 16 h. The acetonitrile was evaporated to dryness, and the residue was washed with dry diethyl ether (3 x 25 mL) in a ultrasonic bath, providing the pure **[bmim][Br]** as a yellow oil (5.20 g, 81 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.98 (t, *J* = 7.3, 3H), 1.42 (m, 2H), 1.94 (m, 2H), 4.13 (s, 3H), 4.34 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 1.8 Hz, 1H), 7.52 (t, *J* = 1.73 Hz, 1H), 10.08 (s, 1H).

1,3-Dibuthylimidazolium iodide [bbim][I]

A solution of 1-butyl-1*H*-imidazole (1.90 g, 15.27 mmol) and 1-iodobutane (5.62 g, 30.52 mmol) in 15 mL of dry ethyl acetate was stirred magnetically at reflux temperature for 6 h. The solvent was evaporated to dryness, and the residue was washed with dry diethyl ether (3 x 25 mL) in a ultrasonic bath, providing the pure **[bbim][I]** as a yellow oil (4.50 g, 96 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.92 (t, *J* = 7.3 Hz, 6H), 1.28-1.41 (m, 4H), 1.83-1.93 (m, 4H), 4.33 (t, *J* = 7.4 Hz, 4H), 7.51 (s, 1H), 7.52 (s, 1H), 10.13 (s, 1H).

1,3-Dibuthylimidazolium bromide [bbim][Br]

A solution of 1-butyl-1*H*-imidazole (0.95 g, 7.64 mmol) and 1-bromobutane (1.04 g, 7.66 mmol) in 20 mL of dry acetonitrile was stirred under reflux for 24 h. The reaction mixture was evaporated to dryness, obtaining the pure **[bbim][Br]** as a yellow oil (1.97 g, 99 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.90 (t, *J* = 7.3 Hz, 6H), 1.38 (m, 4H), 1.90 (m, 4H), 4.35 (t, *J* = 7.4 Hz, 4H), 7.42 (d, *J* = 1.6 Hz, 2H), 10.58 (s, 1H).

1,3-Dimethylimidazolium iodide [mmim][I]

A solution of 1-methyl-1*H*-imidazole (1.83 g, 22.34 mmol) and iodomethane (6.34 g, 44.637 mmol) in 15 mL of dry CH_2Cl_2 was stirred at 0 ºC for 3 h. The reaction mixture was

evaporated to dryness, obtaining the pure **[mmim][I]** as a solid (4.93 g, 99 % yield). Mp: 78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.10 (s, 6H), 7.4 (s, 1H), 7.41 (s, 1H), 10.03 (s, 1H).

General procedure to load anions in AER: A 1% methanolic or hydro-methanolic acid solution or 1 % aqueous ammonium salt solution was passed through a glass column packed with Amberlyst® A-26 (OH^- form) until the pH of eluates was reached to the same value than original solution, and then the resin was washed methanol until neutral pH. The process was carried out at room temperature, using gravity as driving force.

General procedure for anion exchange: A methanolic solution of the imidazolium salt (50-60 mM) was passed through a column packed with Amberlyst A-26, previously loaded with the selected anion, and then washed with 25 mL of methanol. Solvent of the combined eluates were removed, and the oil obtained were dried in a vacuum oven at 60 ºC with P_2O_5 and KOH pellets.

The amount of halide contents in the exchanged ionic liquids was determined by a silver chromate test following a similar protocol described by Sheldon and co-workers.[1] An aqueous solution of potassium chromate (5 % p/v in Milli-Q water, 0.257 M) was added to the sample. A silver nitrate aqueous solution (0.24 % p/v in Milli-Q water, 0.014 M) was added dropwise to 1 mL of the problem solution considering than the end point was reached when a red persistent suspension of silver chromate was observed. Volumes were measured with a 1 ml syringe, and 0.1 mL contains 9 drops of the silver nitrate aqueous solution, consequently 1 drop= 0.011 mL.

[1] A. R. Toral, A. P. de los Rios, F. J. Hernández, M. H. A. Janssen, R. Schoevaart, F. van Rantwijk, R. A. Sheldon, *Enzyme Microb. Technol*., 2007, 40, 1095.

Table S1. Results of the iodide or bromide exchange in imidazolium ionic liquids

compound	[bmim][I] or [Br]		[bbim][I] or [Br]		[mmim][I]	
Anion	Exchange (%)	Yield[a] (%)	Exchange (%)	Yield[a] (%)	Exchange (%)	Yield[a] (%)
AcO^-	100	quant.	100	quant.	100	quant.
BzO^-	100	quant.	100	quant.	100	90
(*S*)-Lactat$^-$	100	quant.	100	quant.	100	quant.
$MeSO_3^-$	100	quant.	100	quant.	100	91
$Bu_2PO_4^-$	100	quant.	100	quant.	100	quant.
F^-	100[b]	82	100[b]	quant.	----	----
Cl^-	100	quant.	100	quant.	100	quant.
PF_6^-	100	quant.	100	quant.	100	quant.
NO_3^-	98	quant.	100	quant.	100	quant.
ClO_4^-	97	quant.	97	quant.	95	quant.
BF_4^-	100	quant.	100	quant.	100	quant.
$H_2PO_4^-$	100	quant.	95	----	100	quant.
HSO_4^-	100	quant.	100	quant.	100	quant.
$CF_3SO_3^-$	100	quant.	100	quant.	100	quant.
$(CN)S^-$	100	quant.	100	quant.	100	quant.

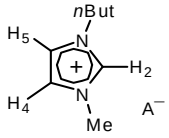
[a] Recovered new ion pair. [b]Analized by HPLC from exchange of Br^- by F^-

Table S2. Halide contents in ionic liquids after anion exchange.[a]

	bmim		bbim		mmim	
Anion	**conc. (mM)**[b]	**I^- (ppm)**[c]	**conc. (mM)**[c]	**I^- (ppm)**[d]	**conc. (mM)**[c]	**I^- (ppm)**[d]
AcO^-	6.05	< 20	4.99	< 20	7.29	< 20
BzO^-	5.76	< 20	4.83	< 20	5.22	< 20
(*S*)-Lactate$^-$	7.27	20-40	3.70	< 20	9.02	< 20
$MeSO_3^-$	4.86	< 20	4.34	< 20	6.97	< 20
$Bu_2PO_4^-$	3.96	< 20	3.74	< 20	4.77	< 20
PF_6^-	4.50	20-40	4.96	< 20	4.13	< 20
NO_3^-	6.36	< 20	6.41	< 20	8.04	20-40
ClO_4^-	5.70	100-120[d]	3.99	20-40[d]	6.82	20-40[d]
BF_4^-	6.19	< 20	5.00	< 20	7.18	20-40
$H_2PO_4^-$	4.91	< 20	3.95	20-40	6.59	< 20
HSO_4^-	6.52	< 20	6.03	20-40	6.18	< 20
$CF_3SO_3^-$	4.37	< 20	4.78	< 20	5.12	< 20

[a] All samples analyzed were obtained from iodide exchange. [b] Concentration of the ionic liquid in the K_2CrO_4 aqueous solution. [c] 1 drop of $AgNO_3$ aqueous solution is enough to react with nearly 20 ppm ($mg \cdot L^{-1}$) of iodide anion. [d] A white suspension was observed and, in the considered end point the $AgCrO_4$ red precipitate surfaced.

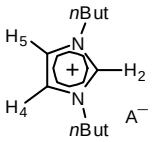
Table S3. ^{1}H NMR chemical shift values of 1-butyl-3-methylimidazolium salts in $CDCl_3$ (300 MHz) at 298 K.[a]



Anion	H_2	H_4	H_5	*n*But	Me	A^-
[AcO^-]	11.44	7.09	7.09	4.30, 1.86, 1.37, 0.97	4.06	2.00
[BzO^-]	11.54	7.09	7.09	4.29, 1.84, 1.33, 0.92	4.08	8.10, 7.33
[S)-lactate$^-$]	11.19	7.17	7.17	4.31, 1.89, 1.38, 0.98	4.08	3.46, 1.41
[$MeSO_3^-$]	10.04	7.25	7.20	4.28, 1.87, 1.38, 0.97	4.05	2.80
[$Bu_2PO_4^-$]	10.19	7.36	7.23	4.25, 1.80, 1.33, 0.88	4.00	3.80, 1.54, 1.33, 0.88
[I^-]	10.10	7.52	7.44	4.35, 1.93, 1.41, 0.99	4.14	
[Br^-]	10.41	7.46	7.37	4.35, 1.91, 1.40, 0.98	4.13	
[F^-]	(b)	7.50	7.33	4.29, 1.87, 1.36, 0.95	4.06	
[Cl^-]	10.99	7.24	7.20	4.34, 1.91, 1.40, 0.98	4.13	
[PF_6^-]	9.19	7.27	7.24	4.22, 1.90, 1.39, 0.98	4.00	
[NO_3^-]	10.02	7.35	7.30	4.25, 1.88, 1.38, 0.97	4.02	
[ClO_4^-]	9.15	7.30	7.26	4.23, 1.89, 1.39, 0.98	4.02	
[BF_4^-]	8.98	7.28	7.24	4.21, 1.87, 1.39, 0.97	3.98	
[HSO_4^-][c]	10.43	7.31	7.31	4.23, 1.78, 1.29, 0.90	3.93	
[$CF_3SO_3^-$]	9.27	7.32	7.28	4.21, 1.88, 1.38, 0.97	3.99	
[SCN^-]	9.59	7.36	7.31	4.32, 1.92, 1.41, 0.99	4.11	

[a] Solution concentrations are 0.02 M. [b]Signal not observed due to H-D exchange. [c]In CD_3CN

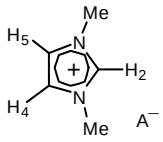
Table S4. ^{1}H NMR chemical shift values of 1,3-dibutylimidazolium salts in $CDCl_3$ (300 MHz) at 298 K.[a]



Anion	H_2	$H_{4,5}$	*n*But	A^-
[AcO^-]	11.32	7.14	4.35, 1.86, 1.39, 0.97	2.01
[BzO^-]	11.40	7.16	4.34, 1.87, 1.35, 0.93	8.10, 7.32
[S)-lactate$^-$]	11.29	7.14	4.33, 1.87, 1.37, 0.96	4.02, 1.39
[$MeSO_3^-$]	9.73	7.51	4.30, 1.88, 1.37, 0.96	2.75
[$Bu_2PO_4^-$]	11.05	7.11	4.37, 1.88, 1.40, 0.94	3.87, 1.62, 1.40, 0.94
[I^-]	10.34	7.38	4.38, 1.95, 1.42, 0.99	
[Br^-]	10.58	7.42	4.36, 1.90, 1.37, 0.95	
[F^-]	(b)	7.17	4.30, 1.89, 1.40, 0.98	
[Cl^-]	11.05	7.23	4.38, 1.92, 1.41, 0.98	
[PF_6^-]	9.05	7.23	4.24, 1.88, 1.39, 0.98	
[NO_3^-]	9.89	7.39	4.25, 1.86, 1.33, 0.94	
[ClO_4^-]	9.24	7.38	4.26, 1.88, 1.37. 0.96	
[BF_4^-]	9.12	7.36	4.23, 1.87, 1.36, 0.95	
[$H_2PO_4^-$]	10.59	7.31	4.40, 1.84, 1.34, 0.92	
[HSO_4^-][c]	10.84	7.40	4.39, 1.84, 1.34, 0.91	
[$CF_3SO_3^-$]	9.49	7.28	4.26, 1.88, 1.38, 0.98	
[SCN^-]	9.18	7.34	4.25, 1.88, 1.38, 0.97	

[a] Solution concentrations are 0.02 M. [b]Signal not observed due to H-D exchange. [c]In CD_3CN

Table S5. ^{1}H NMR chemical shift values of 1,3-dimethylimidazolium salts in CD_3CN (300 MHz) at 298 K.[a]



Anion	H_2	$H_{4,5}$	Me	A^-
[AcO^-]	9.05	7.32	3.83	1.69
[BzO^-]	9.29	7.33	3.85	7.93, 7.28
[S)-lactate$^-$][b]	11.04	7.15	4.03	3.80, 1.38
[$MeSO_3^-$]	8.58	7.33	3.83	2.43
[$Bu_2PO_4^-$] [b]	10.88	7.15	4.04	3.86, 1.61, 1.39, 0.90
[I^-]	8.48	7.34	3.83	
[Cl^-]	8.57	7.34	3.83	
[PF_6^-]	8.38	7.32	3.82	
[NO_3^-]	8.57	7.34	3.83	
[ClO_4^-]	8.45	7.33	3.82	
[BF_4^-]	8.43	7.33	3.82	
[$H_2PO_4^-$] [b]	10.26	7.30	4.09	
[HSO_4^-] [b]	10.19	7.34	4.09	
[$CF_3SO_3^-$]	8.45	7.33	3.82	
[SCN^-]	8.44	7.33	3.83	

[a] Solution concentrations are 0.02 M. [b] In $CDCl_3$

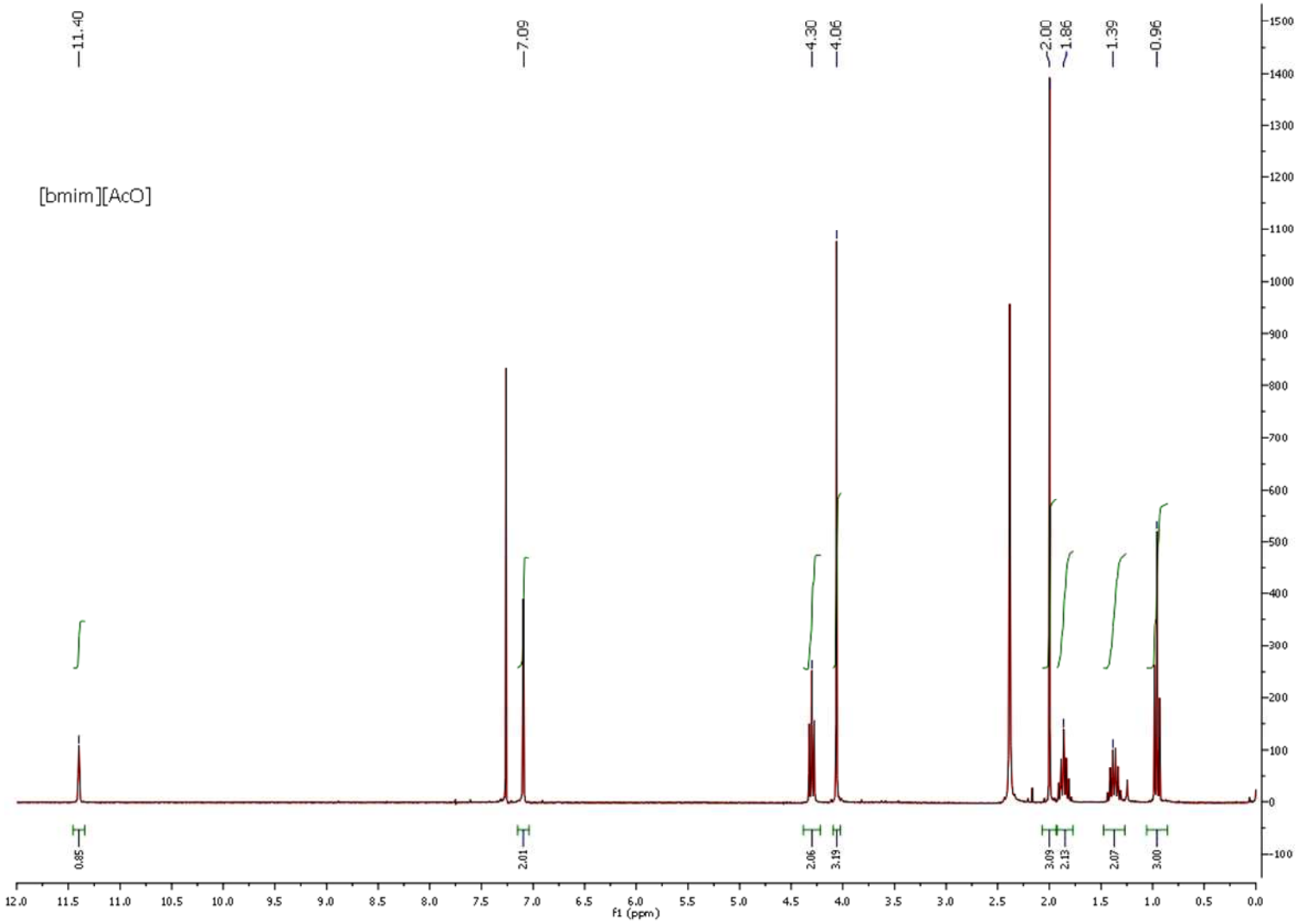


Figure S-1. ^{1}H NMR (300 MHz, $CDCl_3$) of [bmim][AcO]

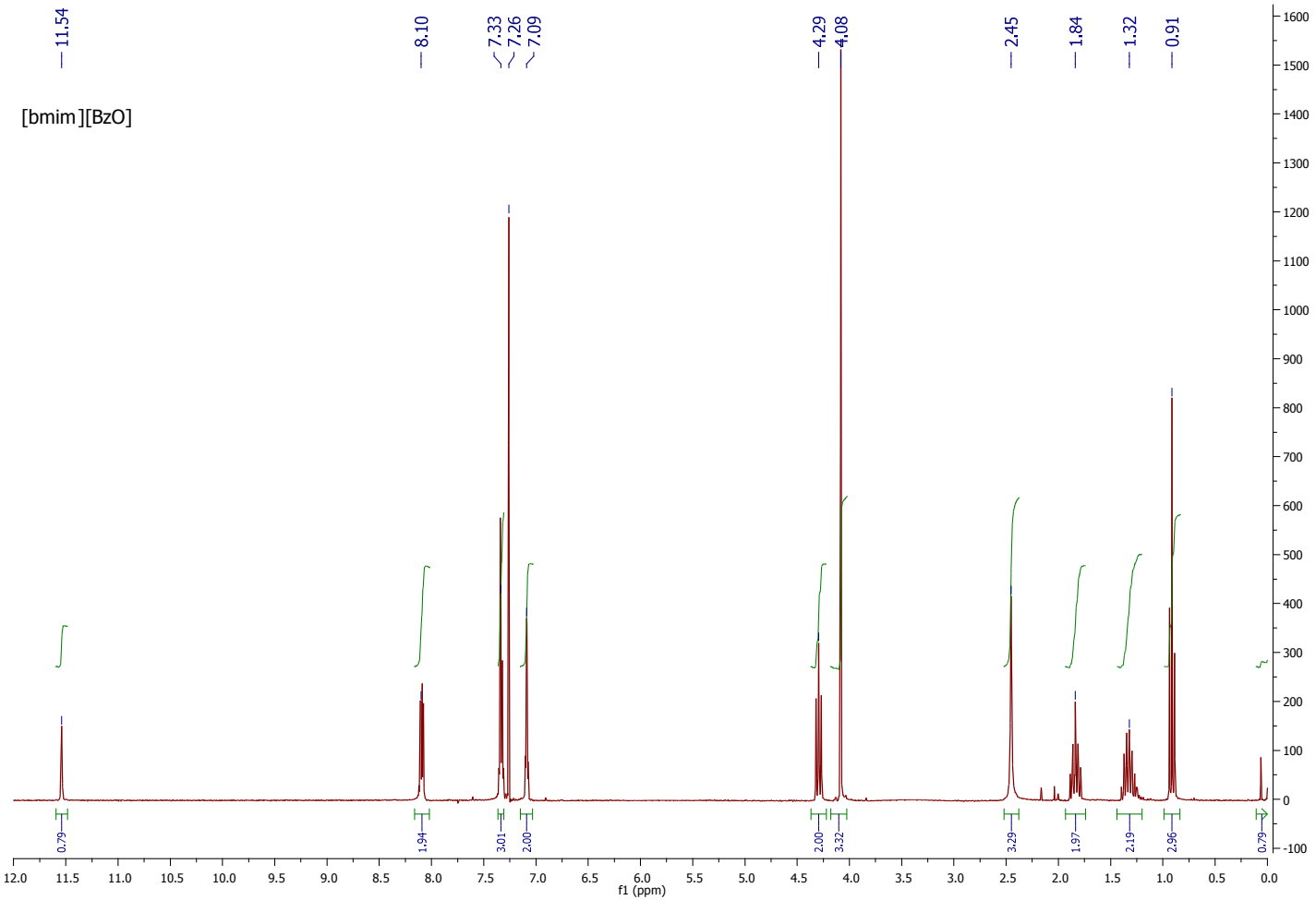


Figure S-2. ^{1}H NMR (300 MHz, $CDCl_3$) of [bmim][benzoate]

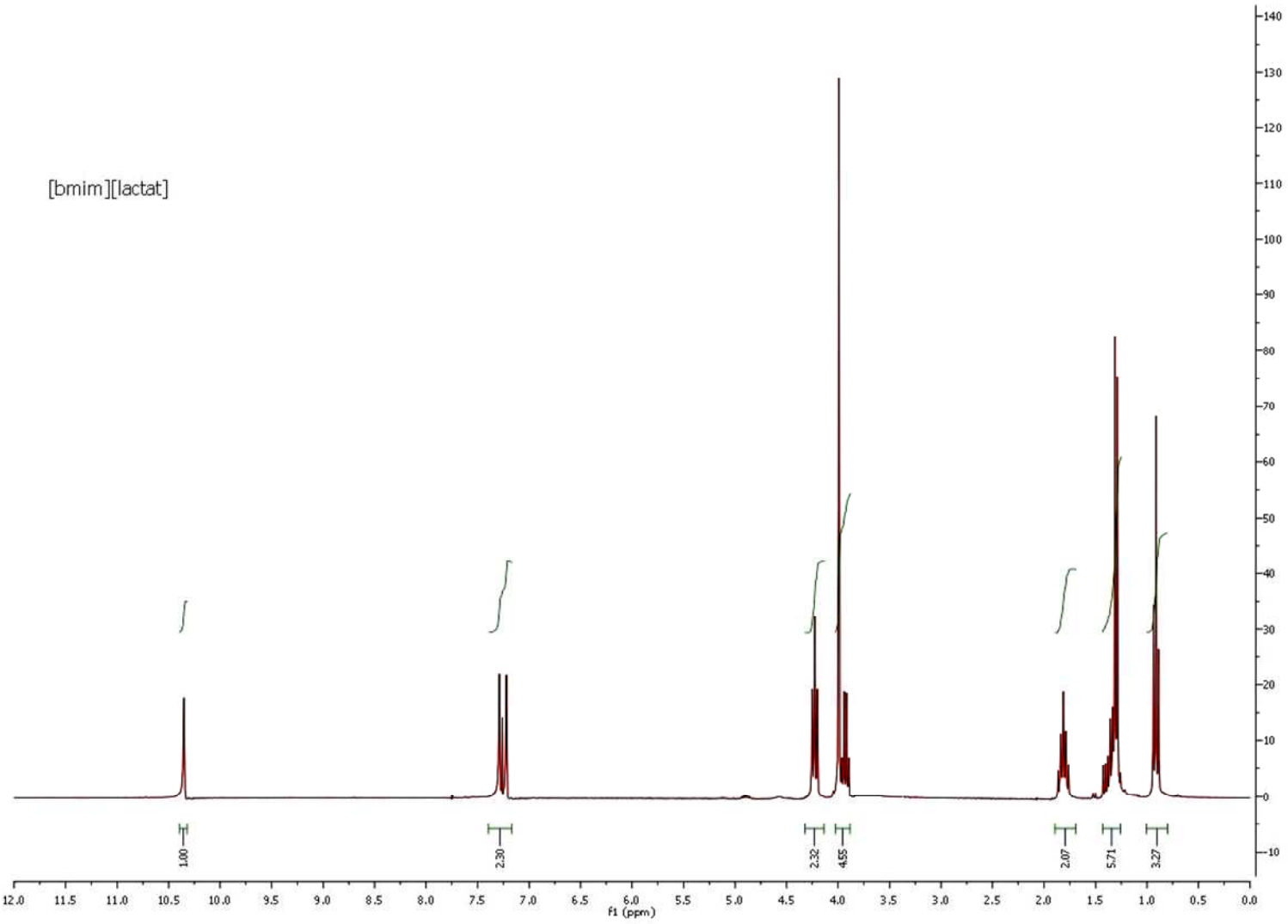


Figure S-3. ^{1}H NMR (300 MHz, $CDCl_3$) of [bmim][(*S*)-lactate]

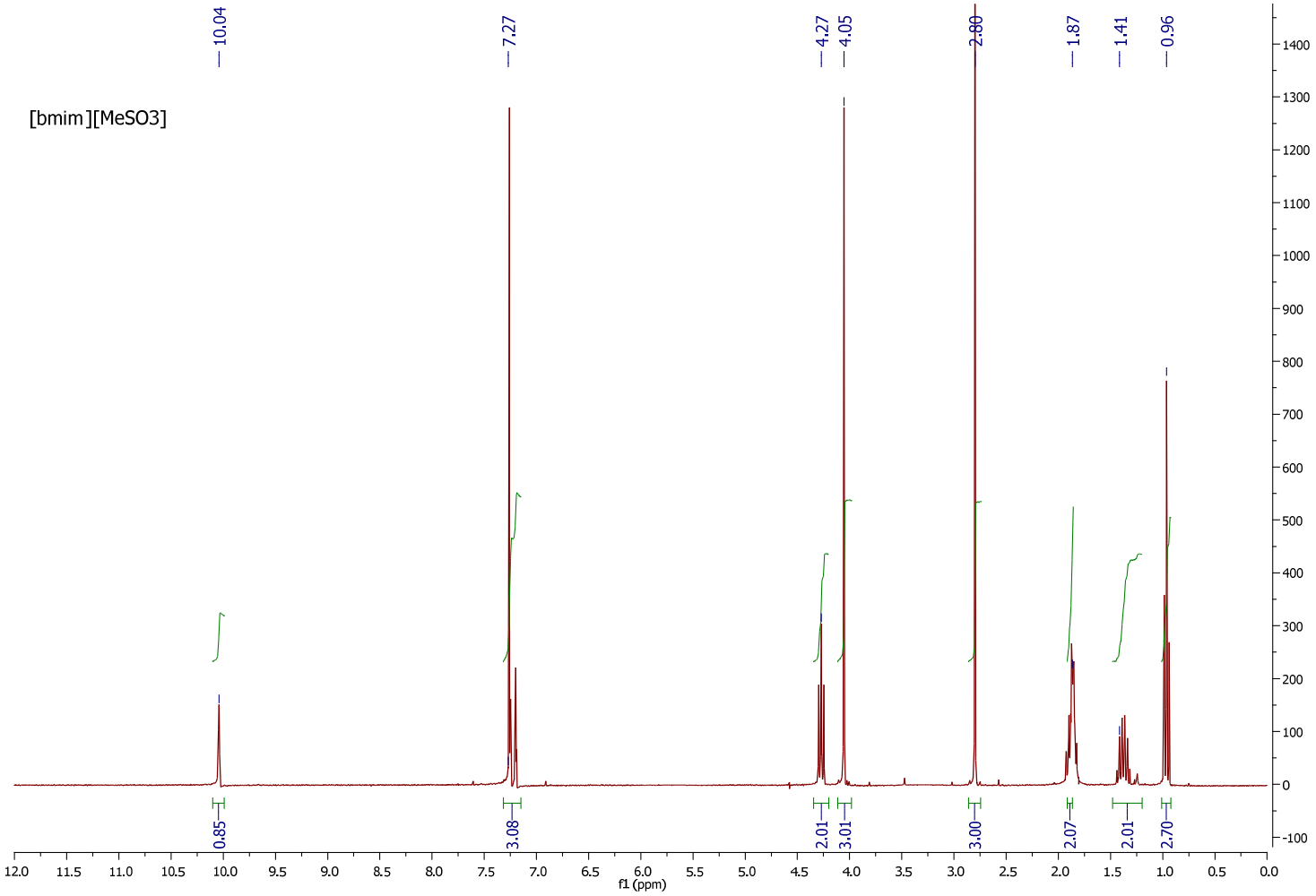


Figure S-4. ^{1}H NMR (300 MHz, $CDCl_3$) of [bmim][CH_3SO_3]

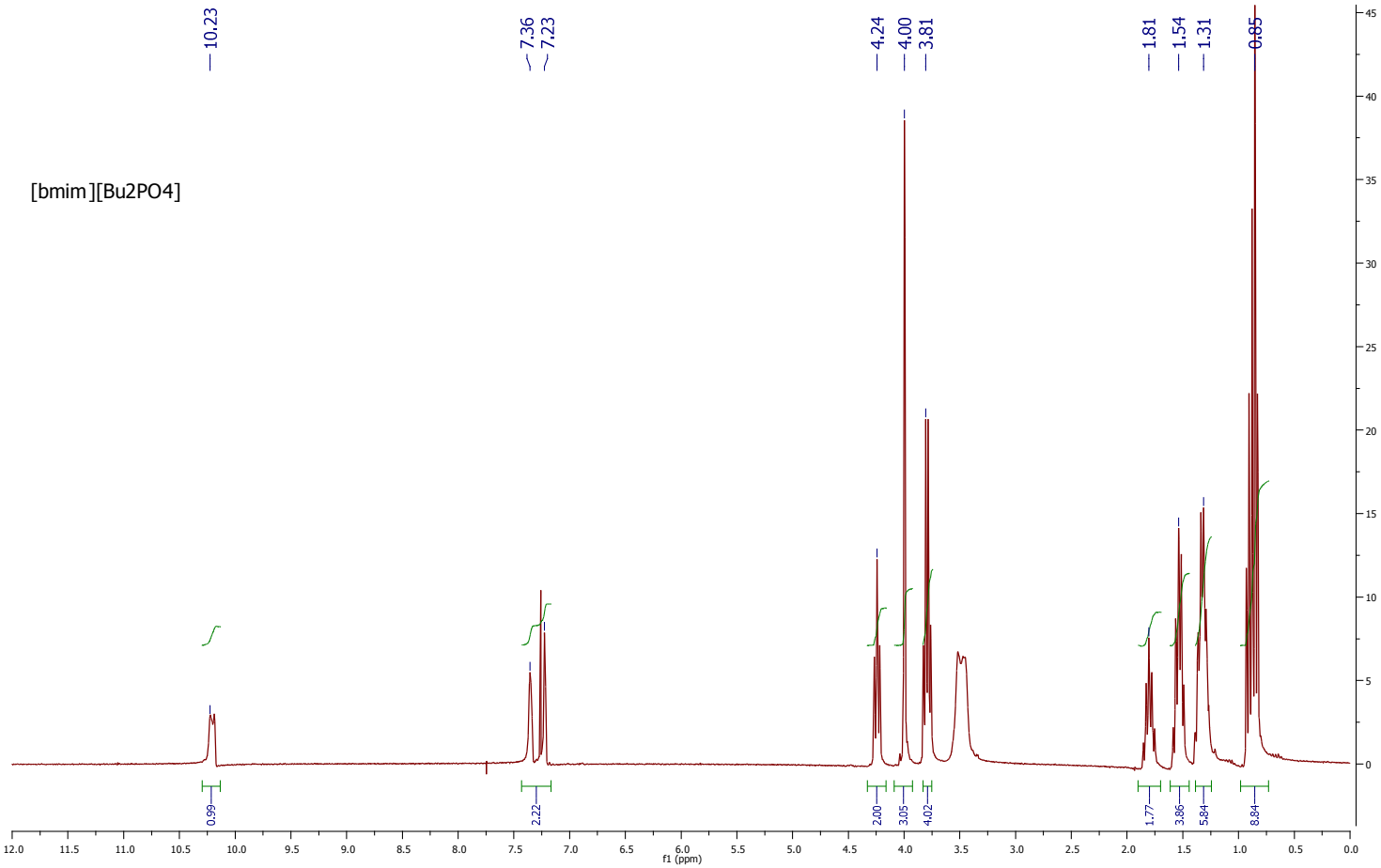


Figure S-5. ^{1}H NMR (300 MHz, $CDCl_3$) of [bmim][Bu_2PO_4]

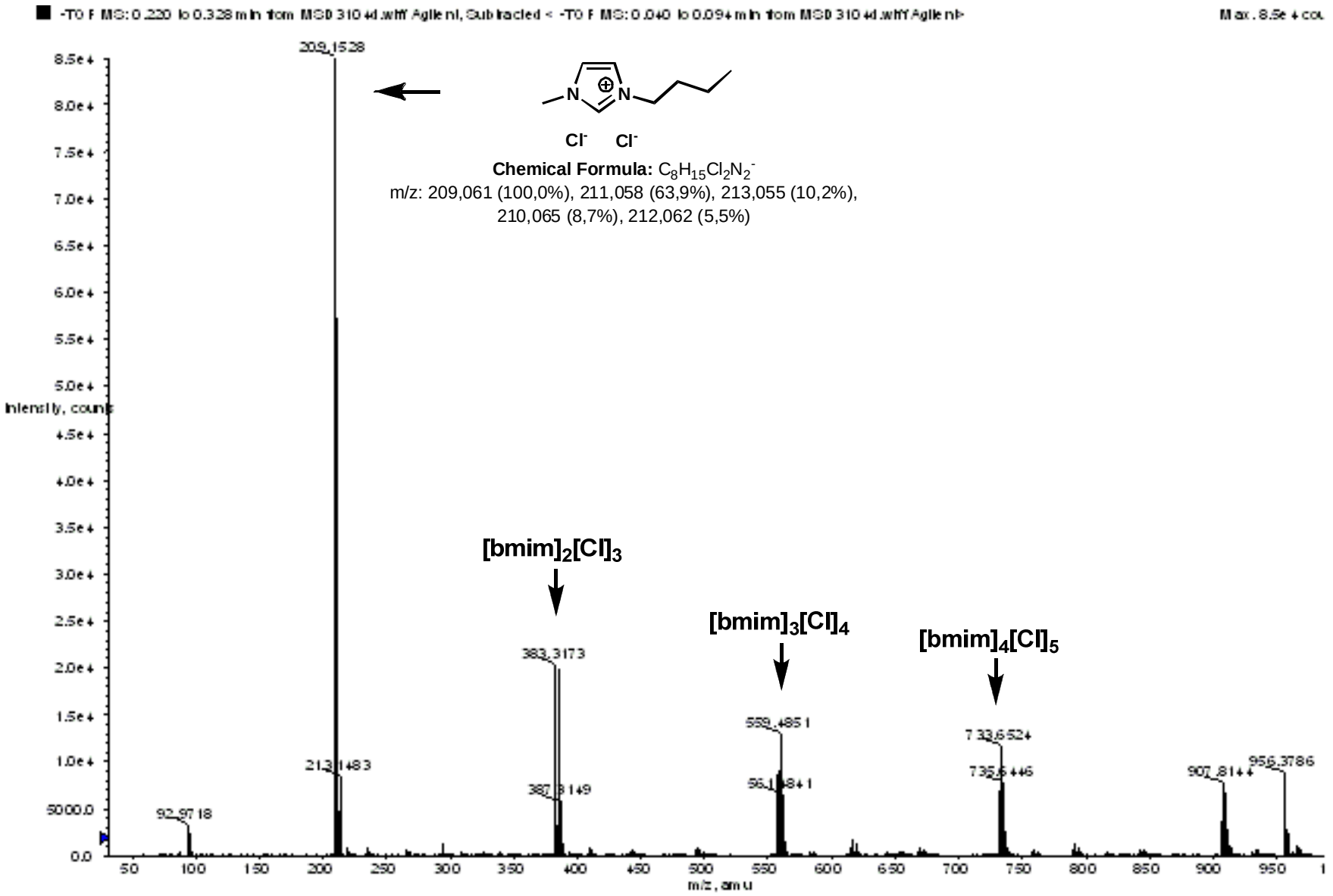


Figure S-6. ESI(-)-MS (175V) [bmim][Cl].

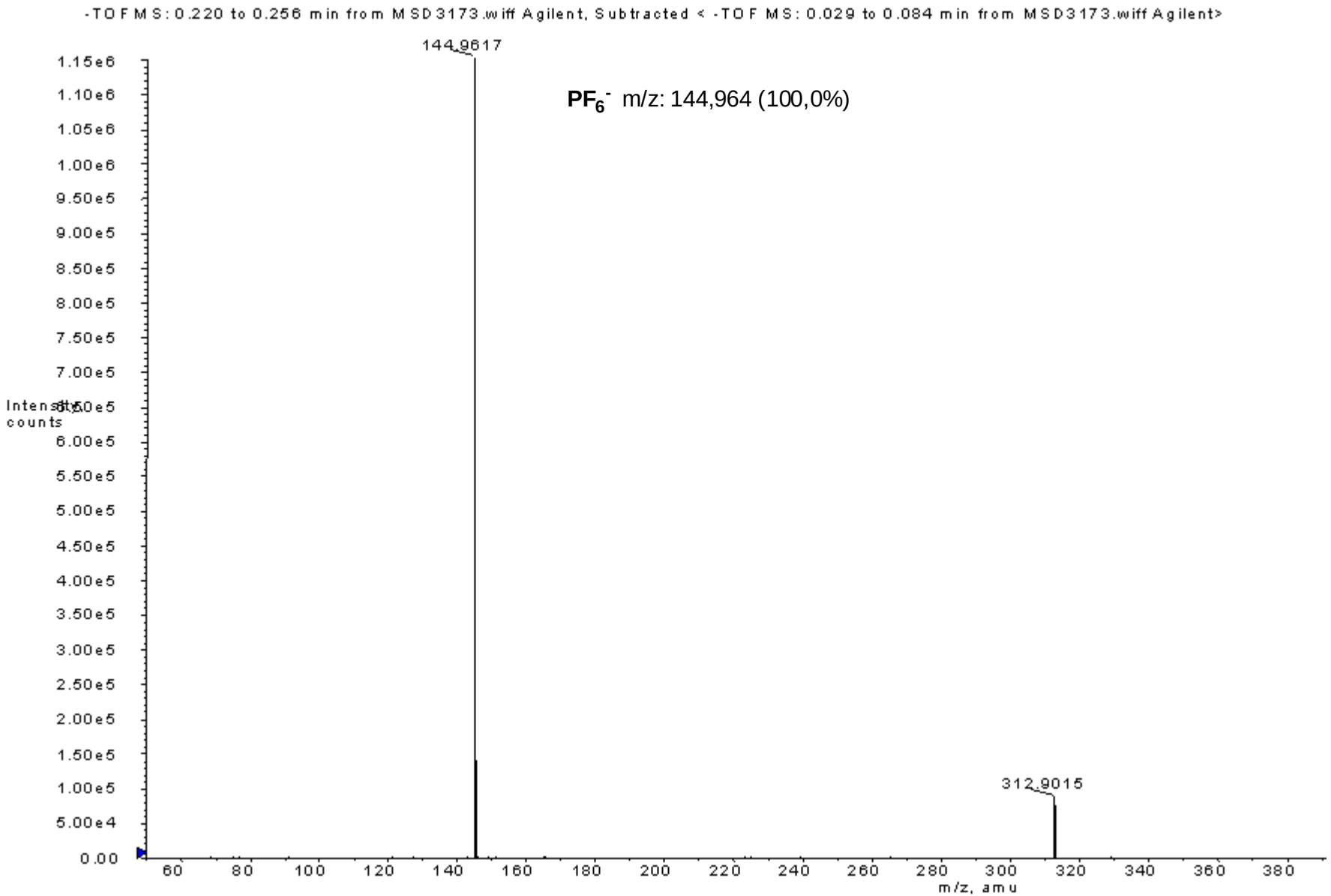


Figure S-7. ESI(-)-MS (175V) [bmim][PF6].

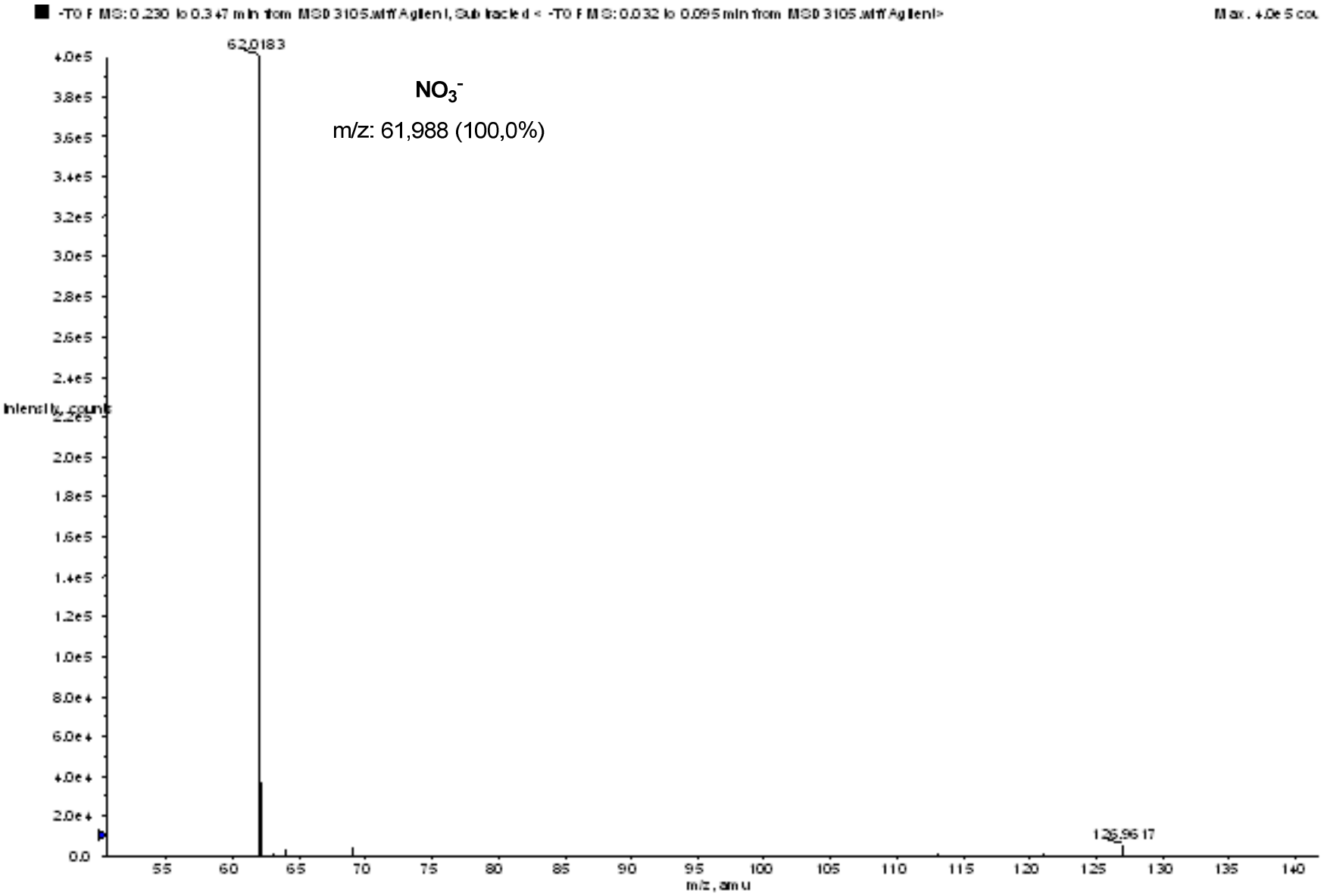


Figure S-8. ESI(-)-MS (175V) [bmim][NO3].

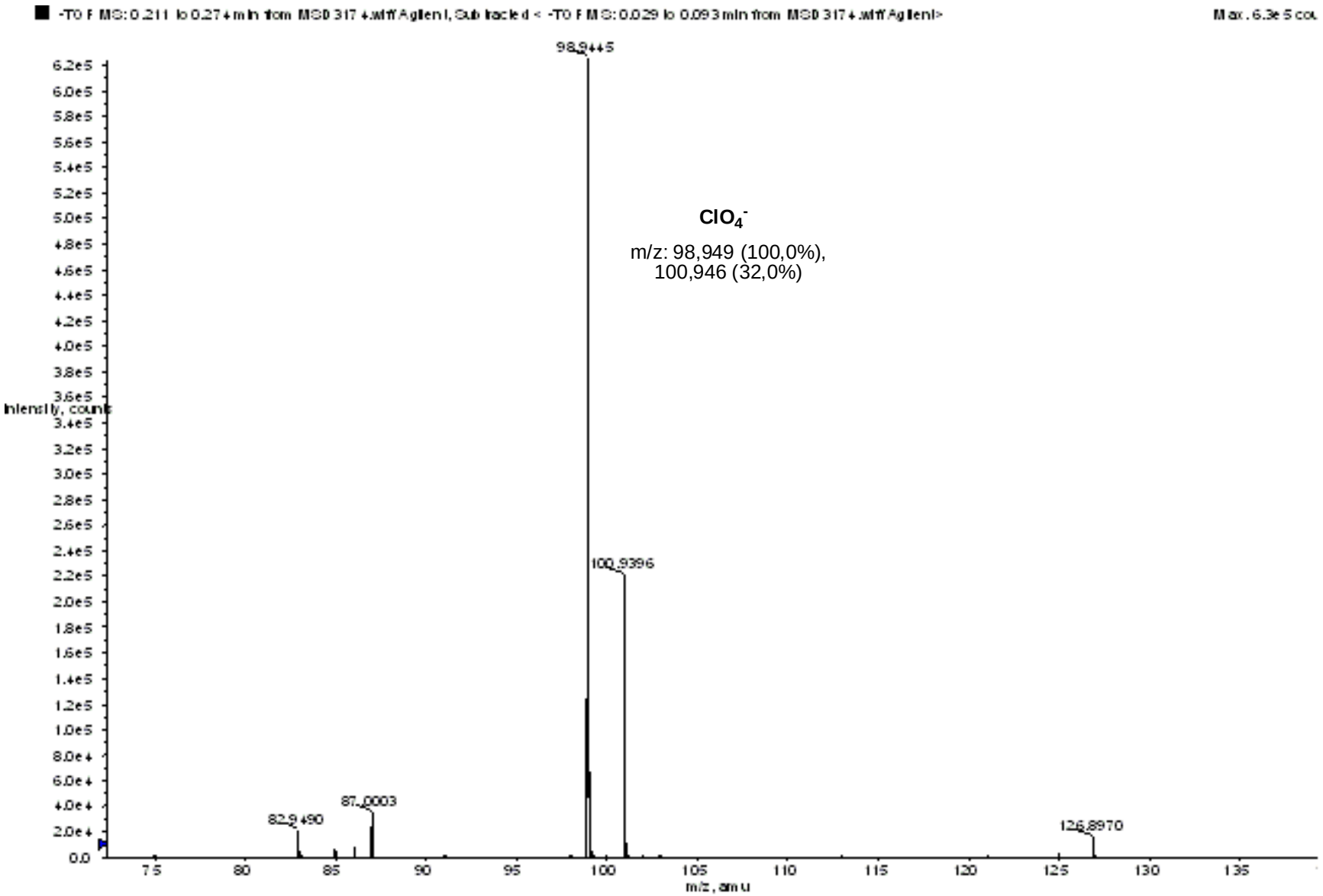


Figure S-9. ESI(-)-MS (175V) [bmim][ClO4].

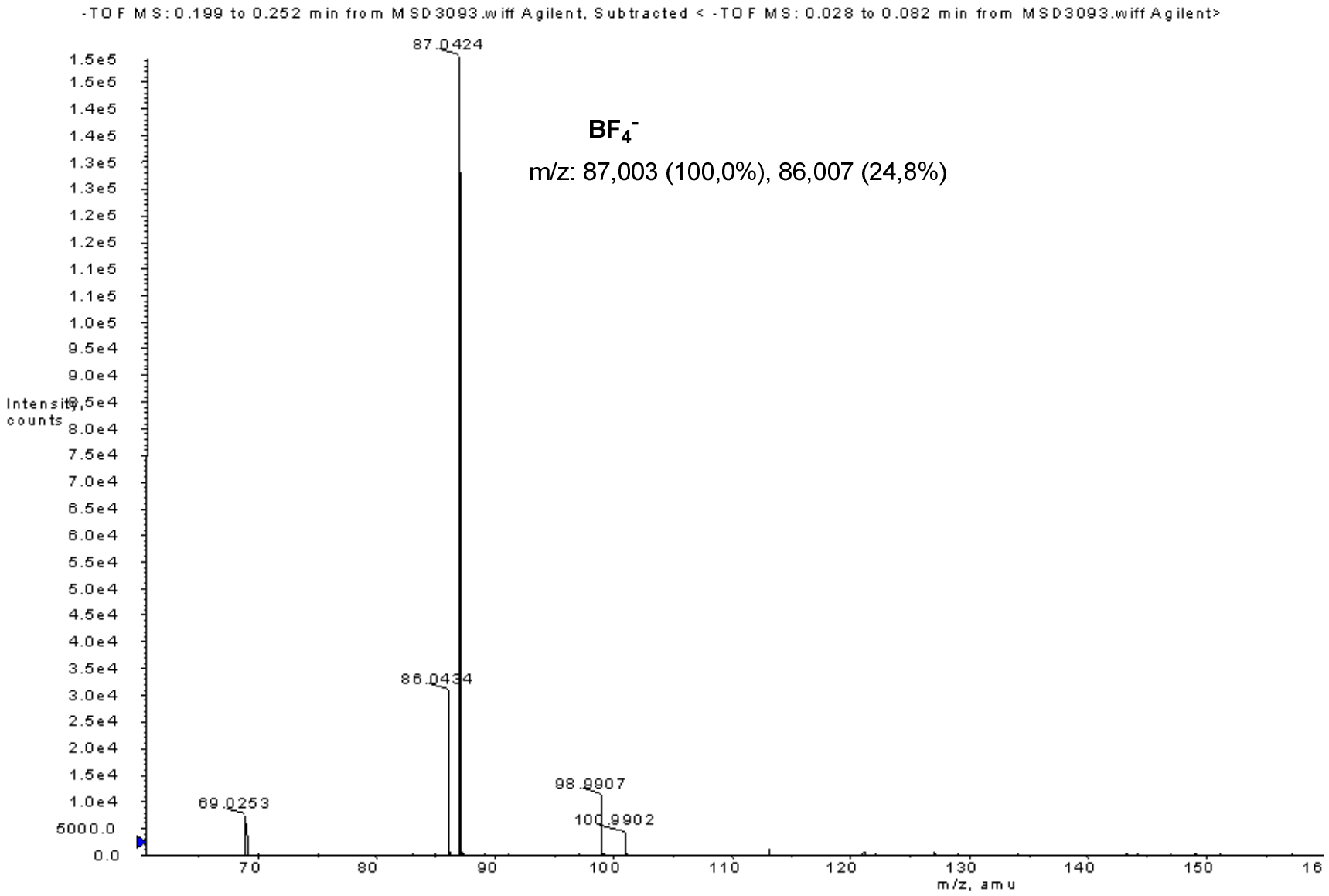


Figure S-10. ESI(-)-MS (175V) [bmim][BF4].

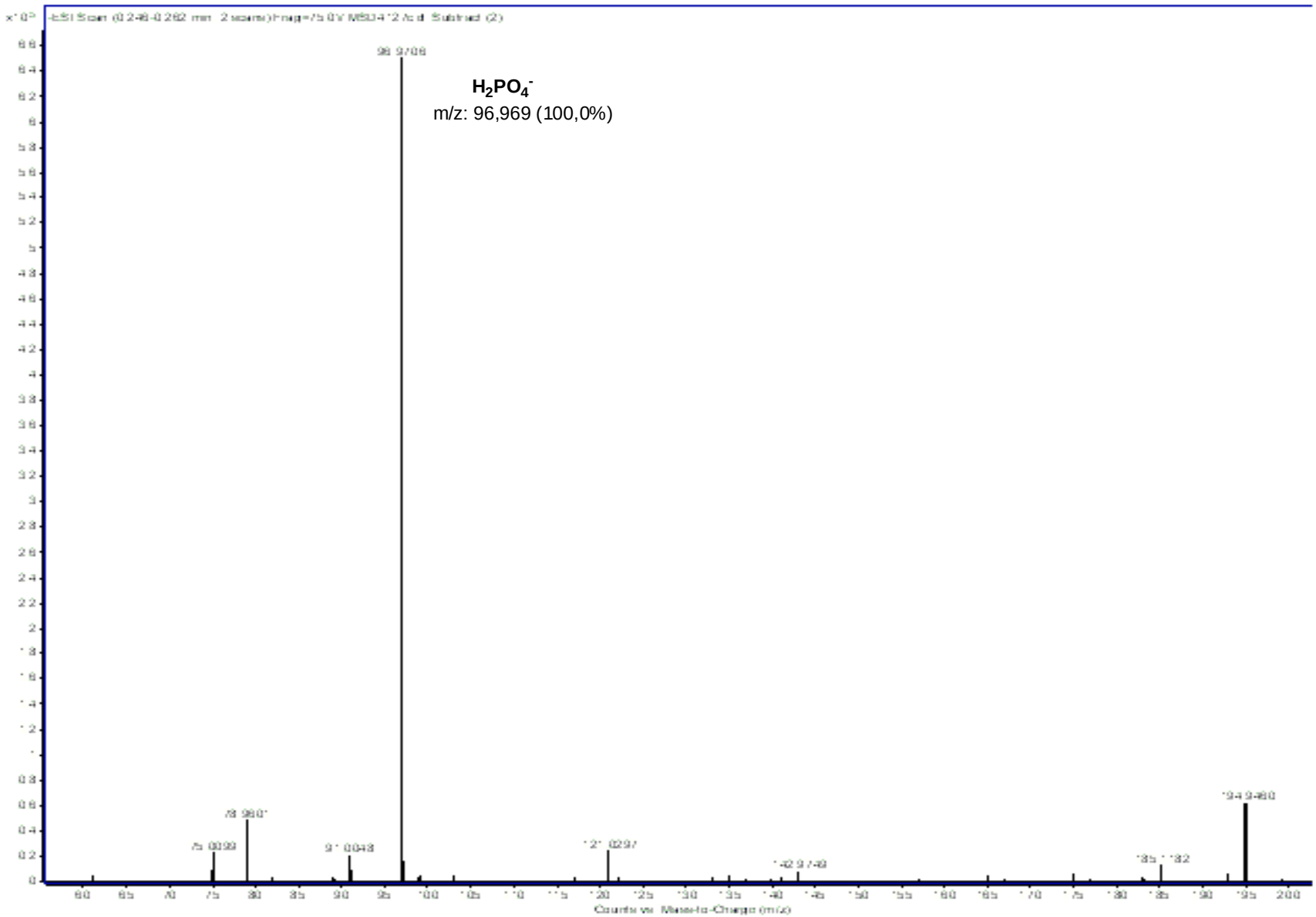


Figure S-11. ESI(-)-MS (75V) [bmim][H2PO4].

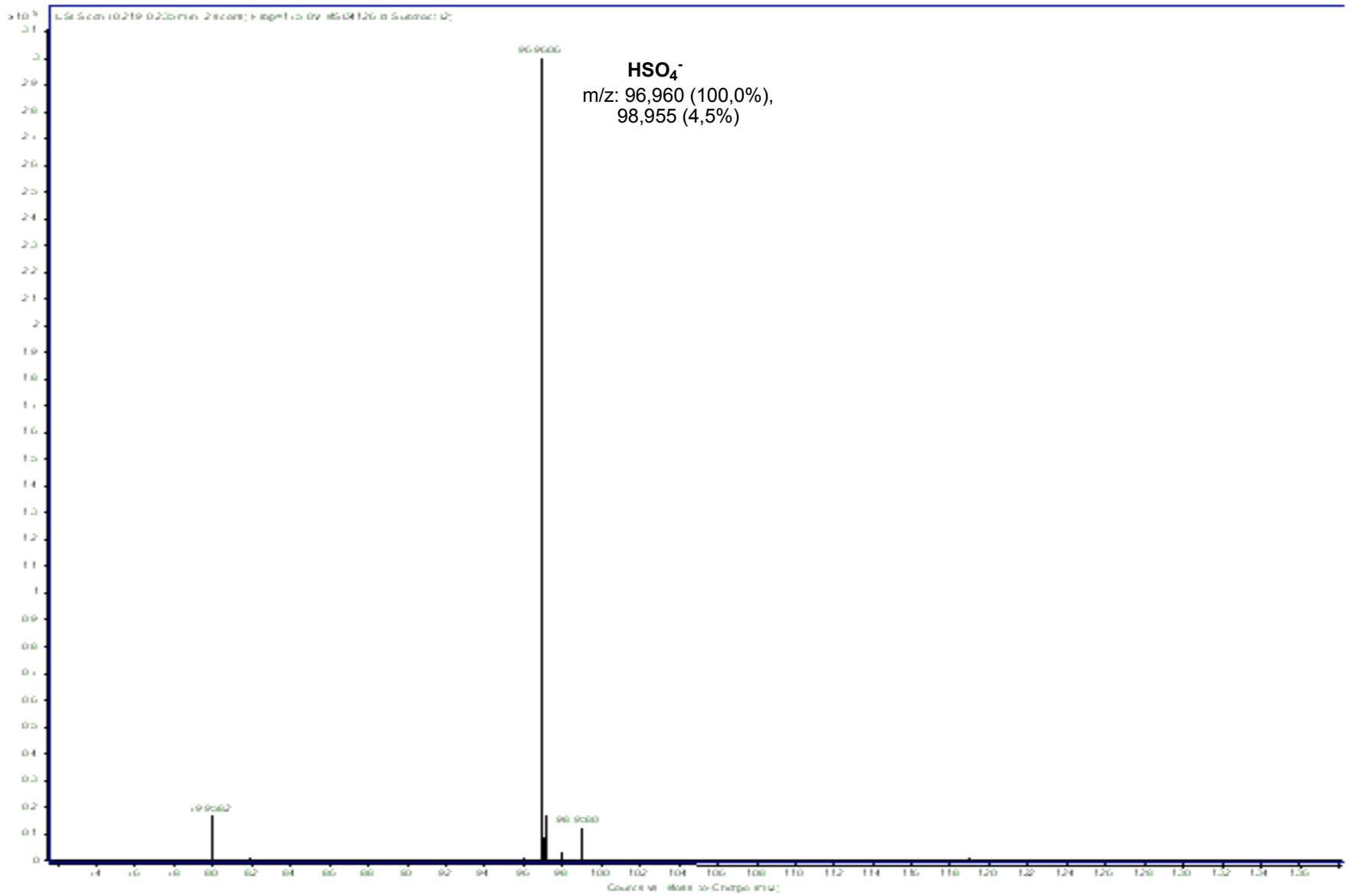


Figure S-12. ESI(-)-MS (75V) [bmim][HSO4].

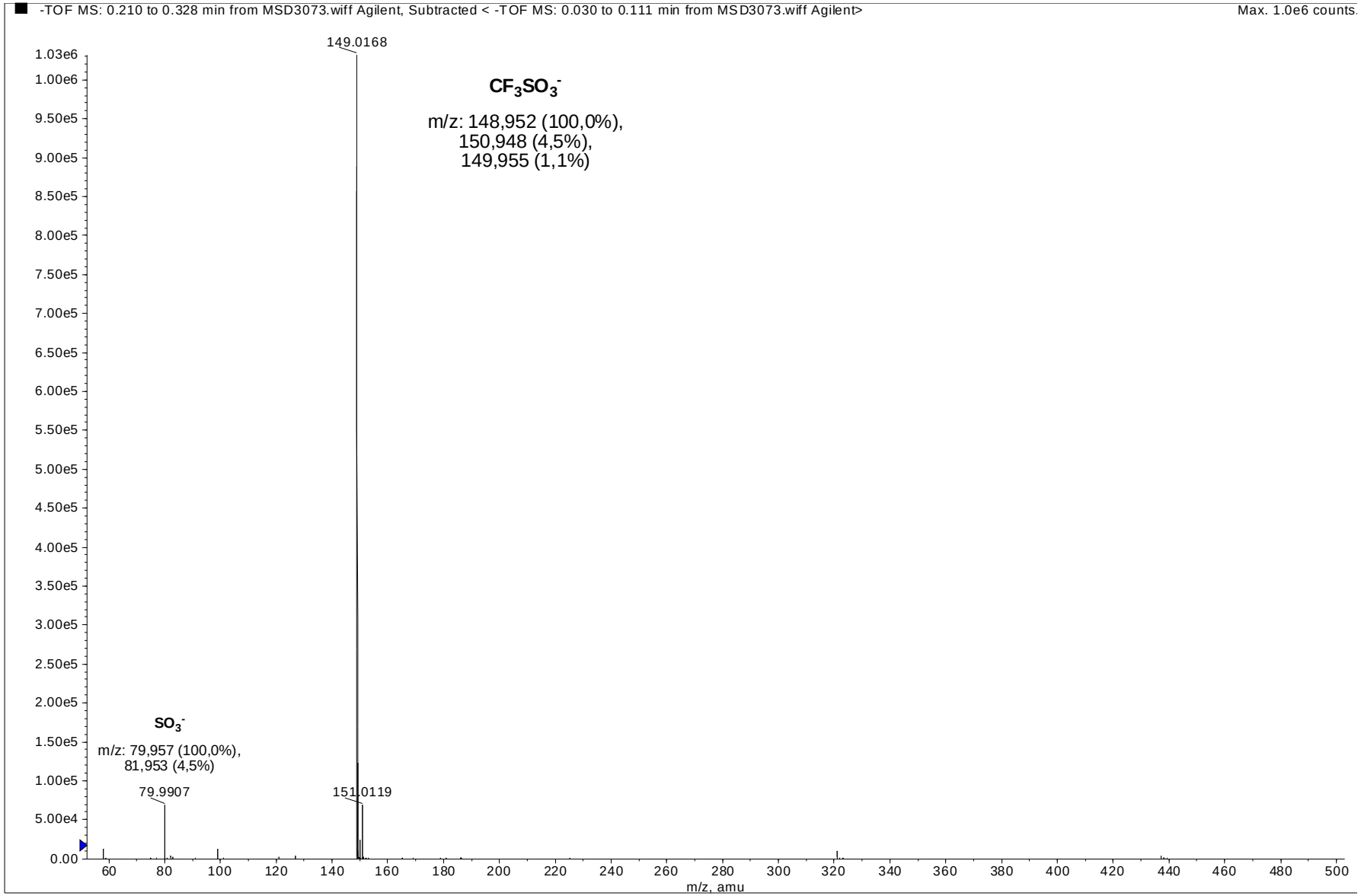


Figure S-13. ESI(-)-MS (175V) [bmim][CF3SO3].

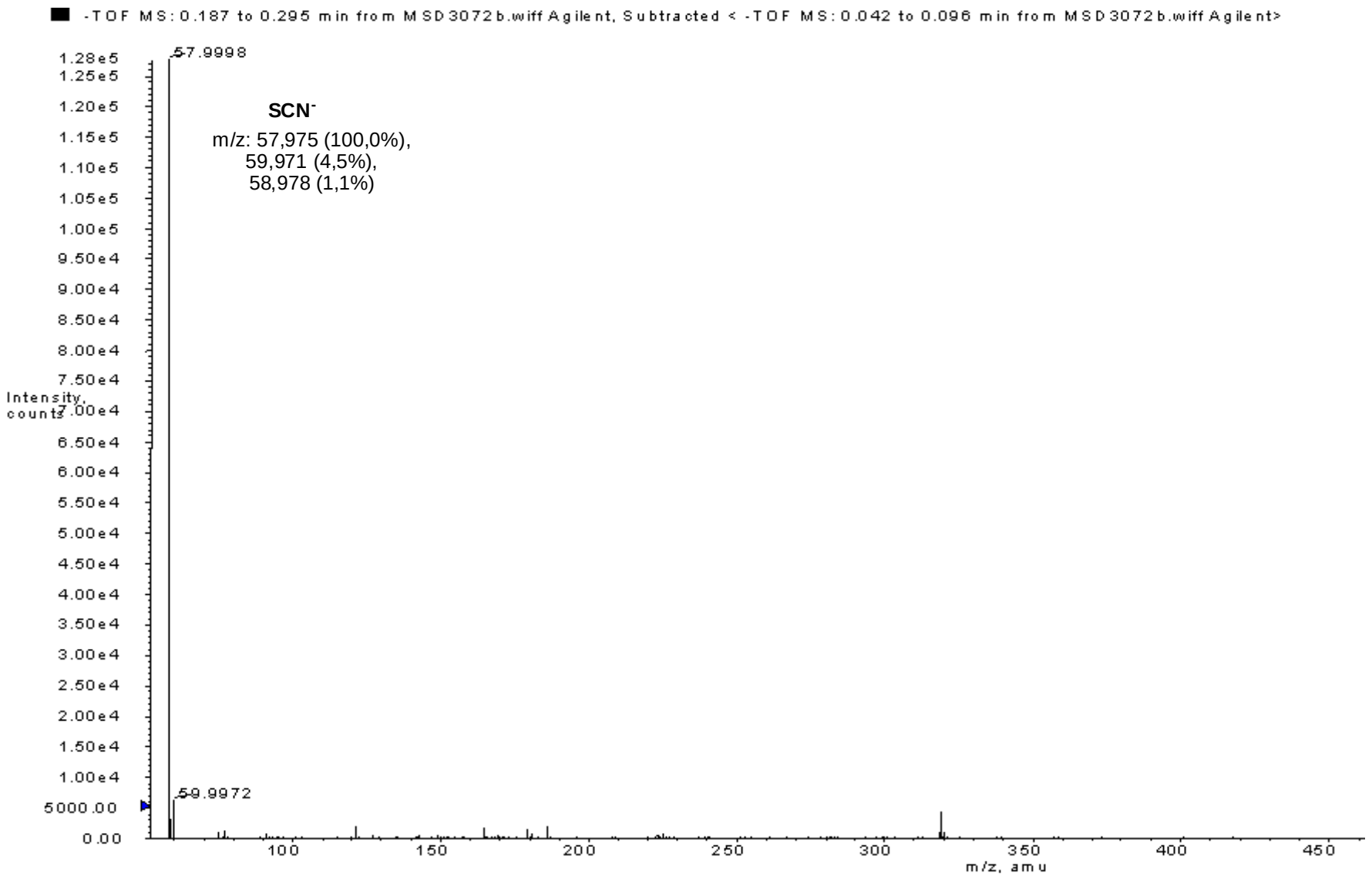


Figure S-14. ESI(-)-MS (175V) [bmim][SCN].

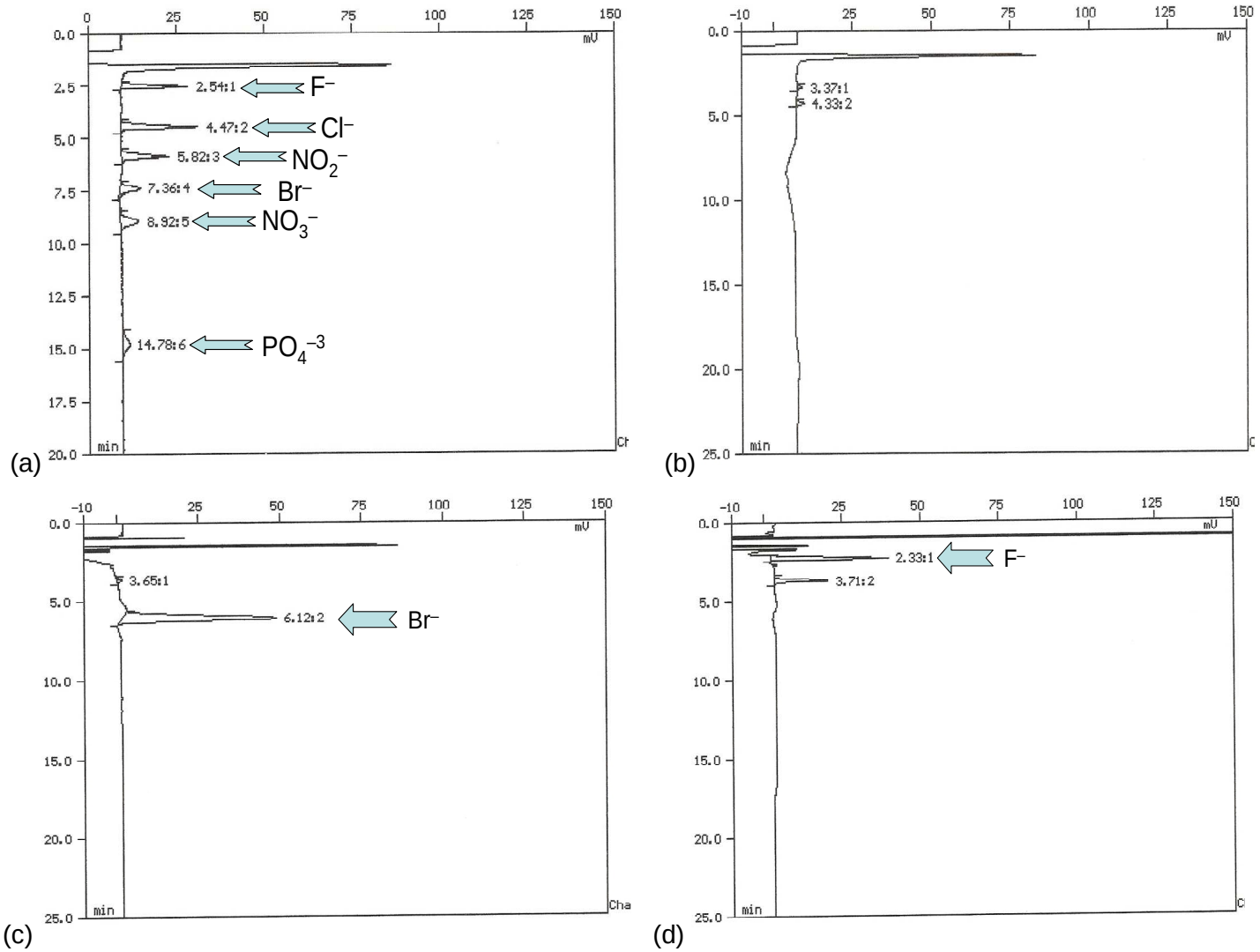


Figure S-15 HPLC-chromatogram of (a) pattern anions; (b) distilled water; (c) [bmim][Br]; (d) [bmim][F] obtained from [bmim][Br].

- **A general halide-to-anion switch for imidazolium-based ionic liquids and oligocationic systems using anion exchange resins (A^- form).**

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COMMUNICATION

A general halide-to-anion switch for imidazolium-based ionic liquids and oligocationic systems using anion exchange resins (A^- form)†‡

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Further studies on the application of an AER (A^- form) method broadened the anion exchange scope of representative ionic liquids and bis(imidazolium) systems. Depending on the hydrophobicity nature of the targeted imidazolium species and counteranions, different organic solvents were used to swap halides for assorted anions, proceeding in excellent to quantitative yields.

The incorporation of imidazolium quaternary salts in a wide array of cationic and oligocationic systems situate them at the crossroads of multidisciplinary fields in chemistry.[2–4] The role of ionic liquids (ILs), besides their increasing importance as green solvents, has been broadened to ionic liquid salt forms of active pharmaceutical ingredients (APIs),[5] energetic ionic liquids (EILs)[6] and tuneable aryl alkyl ionic liquids (TAAILs).[7] Their industrial applications have also been reviewed.[8] Chemical aspects of imidazolium-based ILs concern their preparation, counteranion exchange and purity.[2,9–12]

The common synthetic route to imidazolium-based systems is a subclass of the Menschutkin reaction and gives the targeted imidazolium system in which the counteranions, halide ions, can be exchanged by different methods. A habitual method is to swap the halide ion for another anion using an inorganic salt (MA) that is also used to remove halide ions in ILs. The halide-containing by-product salts can then be eliminated by extraction or precipitation followed by filtration. Overcoming the purification complexity remains a challenging issue with the aim of obtaining pure IL salts, especially halide-free ion pairs.

The apparent directness of the counteranion exchange process does not imply that it is either simple or trivial since isolation and purification of pure heteroaromatic quaternary systems, *e.g.* imidazolium salts, is sometimes difficult and can be a serious problem when the solubility of the different ionic species present in the solution mixture is similar (Scheme S1, ESI‡).[4] A comparative study of the transformation of *N*-azolylpyridinium salts to the corresponding pyridinium azolate betaines showed that the method of choice makes use of a strongly basic anion exchange resin (AER) converted to the hydroxide form.[13] From 1986 onwards, this procedure was then conveniently applied to a variety of *N*-azolylimidazolium salts with several interannular linkers, including aza-analogues of sesquifulvalene with a betaine character.[14] Exploiting our standard anion exchange procedure, AER (OH^- form), the counteranions of different types of bis(imidazolium) cyclophanes, protophanes and calix[4]arenes were exchanged.[15,16] Recently, Rogers and co-workers have reported an imidazolium-based platform for ILs built up from a methyleneimidazolium tetrazolate subunit, and using an AER (OH^- form) to prepare the betaine structural motif.[17]

There are only a few reports on the application of anion exchange resins to imidazolium-based ILs using either an AER (OH^- form) or AER (A^- form) for the counteranion exchange (Scheme S1, ESI‡). Taking advantage of the anion exchange resin (OH^- form) method, Ohno and co-workers prepared Bio-ILs.[18] Likewise, several ionic liquid buffers were prepared.[19] To the best of our knowledge, there are very few examples in open chemistry literature, applying the AER (A^- form) protocol in water or aqueous methanol. Thus, non-aqueous ionic liquids (NAILs) have been prepared using an AER (PO_4^{3-} form).[20] In a likewise manner with an AER ($R/Ar–SO_3^-$ form), several *N*,*N*′-dialkylpyrrolidinium iodides have been transformed to the corresponding mesylate and tosylate salts.[21] Using an AER (CS^- form) loaded with camphorsulfonate anion, both **ILs·OTs**[22] and following a worthless protocol from **ILs·Br**[23] gave the corresponding **ILs·[CS]**. Treatment of **[bmim][Cl]** with several AER (A^- form) produced the anion exchange giving **[bmim][A]**.[24] Recently, we examined the preparation of an AER (A^- form) conveniently loaded with a variety of anions in water and hydromethanolic media. The counteranion exchange of representative ILs was carried out in aqueous methanol or methanol, providing a pure ionic liquid in quantitative yield.[1] Among different purification protocols of imidazolium ILs,[2,9–13] ion exchange resins should be a plausible method of choice although few reports have examined this.[9,12,25]

In this communication, we report our studies focused on extending the scope of the AER (A^- form) method to swap the halide ion for another anion in water or hydromethanolic media to dipolar nonhydroxylic organic solvents, *e.g.* CH_3CN and $CH_3CN : CH_2Cl_2$ (3 : 7), for halide-free synthesis of

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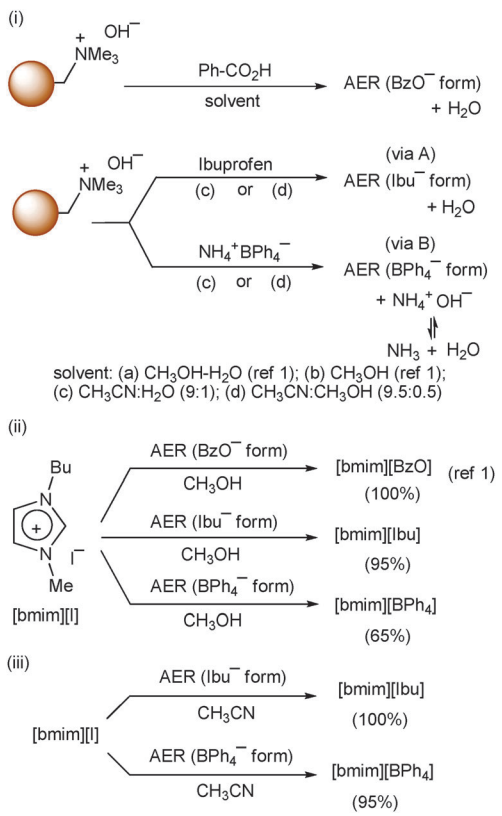
† Imidazolium-based frameworks. 22. Part 21: ref. 1.

‡ Electronic supplementary information (ESI) available: Scheme S1, Tables S1–S5, Fig. S1, experimental procedures and spectral data. See DOI: 10.1039/c0cc05350c

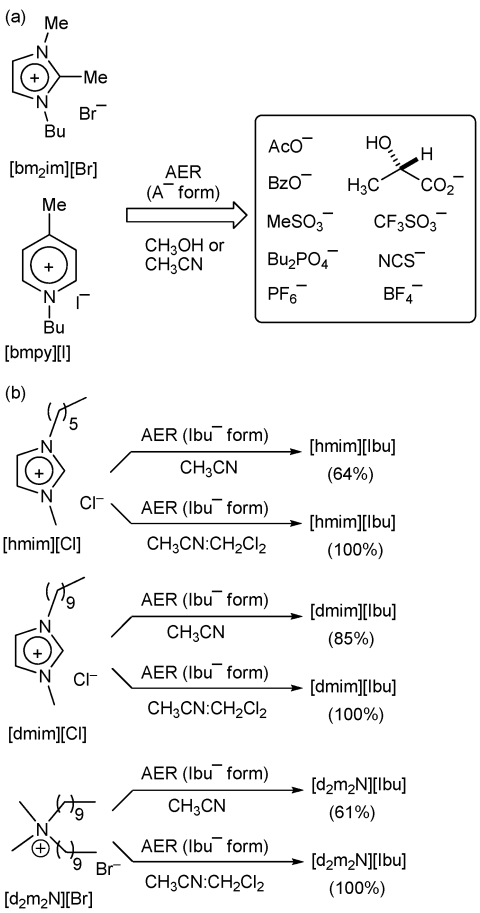
hydrophobic ILs. The usefulness of this procedure has been further developed to hydrophobic bis(imidazolium) systems.

We first examined the AER (OH^- form) loading with acids or ammonium salts using solvent mixtures with different polarities. The column was packed with resin Amberlyst A-26 (OH^- form)[26] and loaded with a 1% benzoic acid solution in different solvents, Scheme 1. The successful loading of solvent mixture CH_3CN : CH_3OH (9.5 : 0.5) afforded AER (Bz^- form) with the lowest proportion of a protic solvent, indicating that a non-aqueous solvent mixture allowed low water-soluble anions to be loaded and only a small proportion of a protic solvent was necessary for the OH^- interchange in the AER. The loading with two selected hydrophobic anions was examined: *via* A, with the anti-inflammatory acid ibuprofen and *via* B, with ammonium tetraphenylborate. The anion loading effectiveness was then checked by passing a methanolic solution of **[bmim][I]** through the AER column loaded with Bz^- anion and the iodide-to-benzoate anion switch proceeded in quantitative yield. Using AER (Ibu^- form) or (BPh_4^- form), the anion exchange in methanol proceeded in 95% and 65% yields, respectively. The test to check anion exchange in acetonitrile for the lipophilic Ibu^- or BPh_4^- anions improved the yield of **[bmim][Ibu]**[27] and **[bmim][BPh_4^-]**[28] to 100% and 95%, respectively (Scheme 1 and Table S1 in ESI‡). Parallel to this work, Viau *et al.*[27] have also reported the preparation of **[bmim][Ibu]** in 94% yield following the classic precipitation procedure from **[bmim][Cl]** (Table S1, ESI‡).



Scheme 1 AER (A^- form) procedure: the loading. (i) Loading the AER (resin (OH^- form) with acids or ammonium salts in different solvent mixtures. (ii) Checking the anion loading. (iii) Testing the anion exchange in CH_3CN.

Next, in order to extend the protocol to less hydrophilic cationic systems, a random of recently reported ILs allowed us to evaluate if the anion exchange was equally successful. Thus, a methanolic solution of **[bm_2im][Br]** or **[bmpy][I]** was passed through a column packed with the convenient AER (A^- form), affording the corresponding pure **[bm_2im][A]** or **[bmpy][A]**, characterized by ^{1}H NMR and ESI(−)-MS. The anion exchange was effective in all cases although in a few assays the yield of the new quaternary salts was only 88%, which was then improved to 100% when the anion exchange was performed in CH_3CN (Scheme 2 and Table S2 in ESI‡). The AER (A^- form) procedure was then applied to representative hydrophobic ILs such as **[hmim][Cl]** and **[dmim][Cl]** together with the quaternary ammonium salt **[d_2m_2N][Br]** to swap the halide for the ibuprofenate anion (Scheme 2 and Table S3 in ESI‡). A solution of the corresponding quaternary salt in CH_3CN was used to perform the anion exchange but the yields were fairly moderate, 64%, 85% and 61% respectively. A more lipophilic solvent mixture of CH_3CN : CH_2Cl_2 (3 : 7) permitted the halide-to-ibuprofenate switch quantitatively, giving the targeted hydrophobic new ibuprofenate imidazolium salts **[hmim][Ibu]** and **[dmim][Ibu]**, and the



Scheme 2 AER (A^- form) procedure in organic solvents: the anion exchange. (a) In CH_3OH or CH_3CN, imidazolium and pyridinium salts: **[bm_2im][Br]**, **[bmpy][I]**. (b) In CH_3CN or CH_3CN : CH_2Cl_2 (3 : 7), imidazolium and quaternary ammonium salts: **[hmim][Cl]**, **[dmim][BrCl]**, **[d_2m_2N][Br]**.

antibacterial–anti-inflammatory salt **[d_2m_2N][Ibu]**, an example of APIs reported by Rogers and co-workers.[5]

Application of our simple halide-to-anion exchange procedure with both lipophilic cations and low hydrophilic anions confirmed its efficiency. Hence, further studies were centered on four examples of less polar imidazolium-based systems (see Fig. S1, ESI‡): the (anthrylmethyl)imidazolium fluorescent chloride **1·Cl**;[29] the known dicationic fluorescent protophane anion receptor **2·2Cl**;[4,30] the bis(imidazolium) cyclophane prototype **3·2Cl**,[4,16] and the new calix[4]arene **4·2Br** (Table S1, ESI‡).

The (anthrylmethyl)imidazolium chloride **1·Cl** was transformed to several fluorescent salts **1·A**, *e.g.* **1·PF_6^-**, **1·BF_4^-**, **1·$CF_3SO_3^-$**, in yields from 70% to 89%, following the classic counteranion exchange with inorganic salts (MA). Accordingly, the ion pair **1·Cl** recently reported by Dyson and co-workers,[29] could be an illustrative example of a less polar simple imidazolium salt to test the efficiency of the AER (A^- form) procedure in organic solvents. When the AER conveniently loaded with PF_6^-, BF_4^- or $CF_3SO_3^-$ anions was used, the anion swap in CH_3OH proceeded in yields from 73% to 93%, whereas a less polar solvent mixture, CH_3CN : CH_3OH (9 : 1) gave nearly quantitative yields of **1·PF_6^-**, **1·BF_4^-** and **1·$CF_3SO_3^-$** (Table S4, ESI‡). Using the same solvent mixture, CH_3CN : CH_3OH (9 : 1), excellent results were obtained for the chloride-to-anion switch of bis(imidazolium) protophane **2·2Cl** and cyclophane **3·2Cl** with a variety of anions to afford **2·2A** and **3·2A**, respectively. The less polar example, the new bis(imidazolium) calix[4]arene **4·2Br** was directly examined in CH_3CN solution and the exchange with representative anions such as AcO^-, BzO^- $MeSO_3^-$, $Bu_2PO_4^-$and PF_6^- proceeded in nearly quantitative yields (Table S5, ESI‡).

In summary, the reported anion exchange resin (A^- form) procedure in non-aqueous media is a simple method of choice to swap the halide ions for a broad range of anions in ionic liquids, concomitantly removing halide impurities. Depending on the hydrophobic nature of the imidazolium salt, different solvents were used, such as CH_3CN and the mixture CH_3CN : CH_2Cl_2 (3 : 7). The halide ion swap procedure progressed in excellent to quantitative yields with both lipophilic imidazolium species and low hydrophilic anions. This anion exchange procedure could be adapted to a diversity of charged molecules such as oligocationic imidazolium systems, along with quaternary heteroaromatic and ammonium salts, thereby developing its performance in fields with still broad scope and unexplored applications such as ionic liquids and anion recognition chemistry.

This research was supported by Vicerrectorat de Recerca, Universitat de Barcelona and by the D.G.I. (*MICINN*) Project CTQ2010-15251/BQU. Thanks are also due to the AGAUR (Generalitat de Catalunya), *Grup de Recerca Consolidat* 2009SGR562.

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Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

A general halide–to–anion switch for imidazolium-based ionic liquids and oligocationic systems using anion exchange resins (A^- form)

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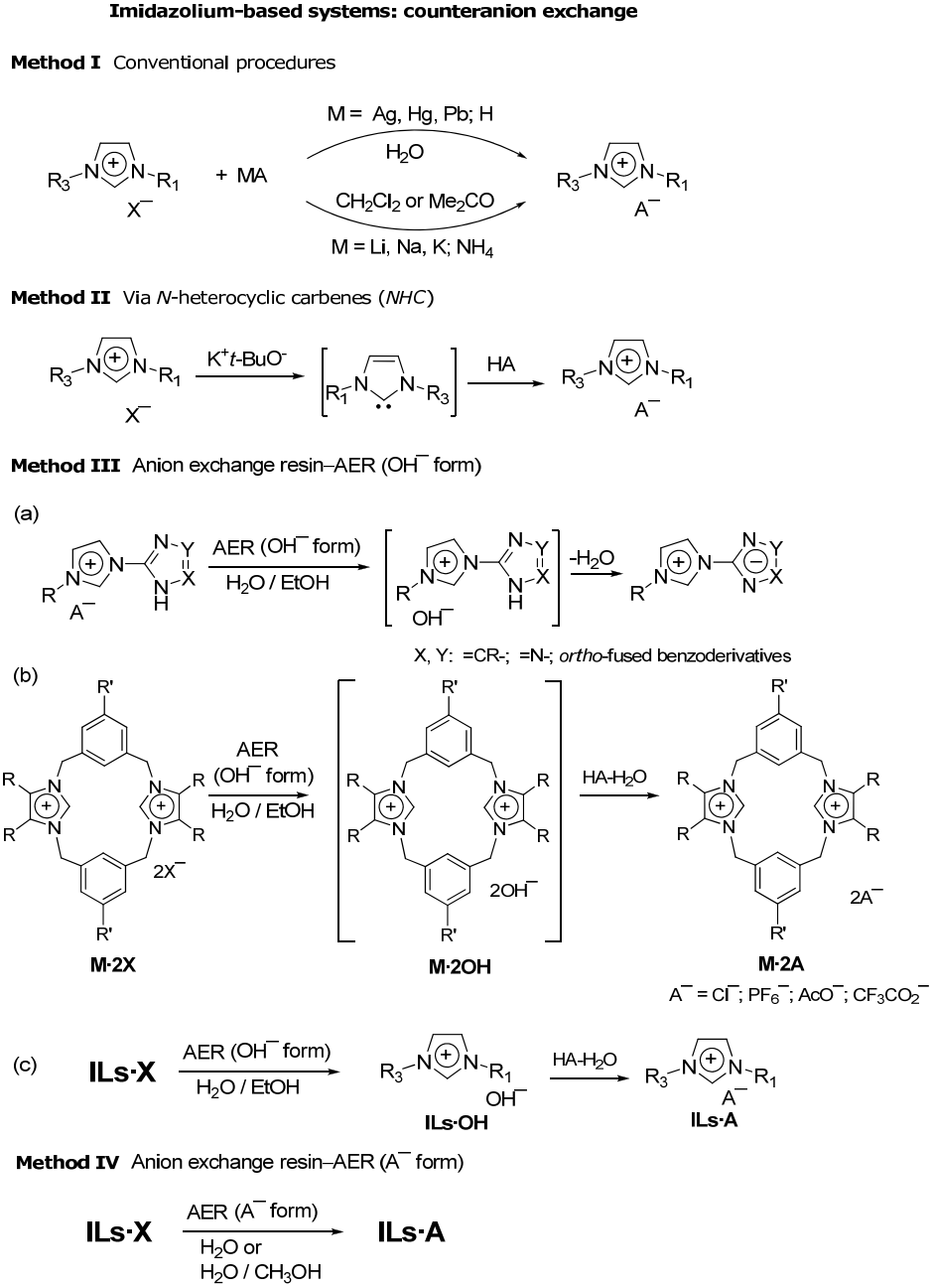


Scheme S1 Imidazolium-based systems: counteranion exchange [ref 4]

Method I

Method II, via *NHC*. [ref 9] and Earle MJ, Seddon KR (2001) Preparation of imidazole carbenes and the use thereof for the synthesis of ionic liquids. [World Patent WO 2001077081 A1].

Method III, anion exchange resin antecedents —AER (OH^- form).

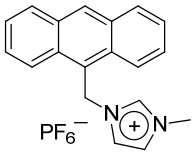
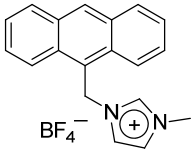
(a) Early studies, *N*-azolylimidazolium and *N*-azolylpyridinium salts. [refs 13,14]

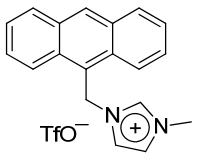
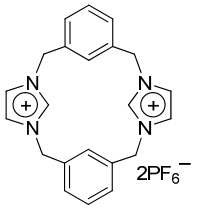
(b) Application to bis(imidazolium) cyclophanes. [refs 15,16]

(c) Application to imidazolium ILs. [ref 18]

Method IV, anion exchange resin —AER (A^- form). [refs 1,19]

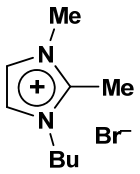
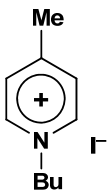
Table S1. Comparison of counteranion exchange procedures and results

Compound	**Reference** [a]		**Our protocol**
[bmim][Ph_4B]	ref 28	**[bmim][Cl]→[bmim][Ph_4B]** 90% $NaPh_4B$ was added to a solution of **[bmim][Cl]** in acetone. After 24 h the reaction mixture was filtered through a plug of Celite®, and the volatiles were removed under reduced pressure.	[I]→[Ph_4B] 65% CH_3OH [I]→[Ph_4B] 95% CH_3CN See Scheme 1 in text
[bmim][Ibu]	ref 27	**[bmim][Cl]→[bmim][Ibu]** 94% A **[bmim][Cl]** ethanolic solution was added slowly to a solution of NaIbu in ethanol and stirred at room temperature for 2 h. The solution was filtered on Millipore® and acetone was added leading to the precipitation of NaCl which was further filtered and the solvent was removed under vacuum.	[I]→[Ibu] 95% CH_3OH [I]→[Ibu] 100% CH_3CN See Scheme 1 in text [Cl]→[Ibu] 100% CH_3CN
[d_2m_2N][IBu]	ref 5	**[d_2m_2N][Br]→[d_2m_2N][Ibu]** 91% **[d_2m_2N][Br]** was dissolved in distilled water by gentle heating and stirring. NaIbu was dissolved in distilled water by gentle heating and stirring. The two solutions were combined and the reaction mixture was heated and stirred for 30 min. Afterwards, the reaction mixture was cooled to room temperature, $CHCl_3$ was added, and the mixture was stirred for an additional 30 min. The two phases were separated and organic phase was washed several times with cool distilled water. The solvent was removed under vacuum.	[Br]→[Ibu] 61% CH_3CN [Br]→[Ibu] 100% CH_2Cl_2:CH_3CN (7:3) See Scheme 2 in text
 **1·PF_6**	ref 29	**1·Cl→1·PF_6** 89% A mixture of **1·Cl** and KPF_6 in water (15 mL) was stirred at room temperature in the dark for 4 h. The reaction mixture was then filtered and the solid product was washed with water and air dried.	[Cl]→[PF_6] 70% CH_3OH [Cl]→[PF_6] 98% CH_3CN:CH_3OH (9:1) See Table S4
 **1·BF_4**	ref 29	**1·Cl→1·BF_4** 70% A mixture of **1·Cl** and $NaBF_4$ in acetone was stirred at room temperature in the dark for 24 h. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The solid obtained was dissolved in dichloromethane and stored at –22ºC for 24 h. After filtration the solvent was removed.	[Cl]→[BF_4] 78% CH_3OH [Cl]→[BF_4] 100% CH_3CN:CH_3OH (9:1) See Table S4

 **1·TfO**	ref 29	**1·Cl→1·TfO** 72% A mixture of **1·Cl** and $LiSO_3CF_3$ in dichloromethane was stirred at room temperature in the dark for 24 h. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The solid obtained was dissolved in dichloromethane and stored at –22ºC for 24 h. After filtration the solvent was removed.	[Cl]→[TfO] 93% CH_3OH [Cl]→[TfO] 95% CH_3CN:CH_3OH (9:1) See Table S4
 **3·2PF$_6$**	ref 16	**3·2Cl→3·2PF$_6$** 91% Treatment of **3·2Cl** with a strongly basic anion-exchange resin (OH^- form) followed by immediate collection of the eluates in aq. HPF_6 to pH = 3.	[Cl]→[PF_6] 63% CH_3OH [Cl]→[PF_6] 95% CH_3CN:CH_3OH (9:1) See Table S5

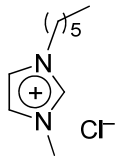
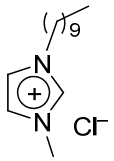
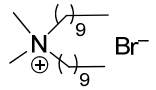
[a] Corresponding reference cited in the text.

Table S2. Results of the halide exchange in imidazolium and pyridinium ionic liquids in methanolic or acetonitrile solution.

compound	 [bm$_2$im][Br]		 [bmpy][I]	
Anion	(%)[a]	**Br$^-$** (ppm)[b]	(%)[a]	**I$^-$** (ppm)[b]
AcO$^-$	98	<13	84 [100][c]	<20
BzO$^-$	100	<13	100	<20
(*S*)-Lactate$^-$	100	<13	100	<20
$MeSO_3^-$	92 [100][c]	<13	100	<20
$Bu_2PO_4^-$	100	<13	100	<20
PF_6^-	91 [100][c]	<39	100	<20
BF_4^-	97	<39	98	<40
$CF_3SO_3^-$	100	<13	100	<20
NCS$^-$	100	ND	100	ND

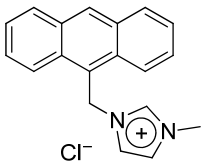
NT: Not Determined [a]Yield of the recovered new ion pair. Yields ≥95 % in CH_3OH were not further investigated. [b]Halide contents after anion exchange determined by silver chromate test; 0.011 mL of $AgNO_3$ aqueous solution is enough to react with nearly 13 ppm (mg·L^{-1}) of bromide anion, or 20 ppm (mg·L^{-1}) of iodide anion.[c]Anion exchange carried out in CH_3CN.

Table S3. Comparative results of anion exchange carried out in CH_3CN or CH_3CN:CH_2Cl_2 mixture.

compound	 [hmim][Cl] C_6mim			 [dmim][Cl] C_{10}mim			 didecyldimethyl ammonium bromide		
Anion	CH_3CN (%)[a]	CH_2Cl_2: CH_3CN (%)[a,b]	**Cl^-** (ppm)[c]	CH_3CN (%)[a]	CH_2Cl_2: CH_3CN (%)[a,b]	**Cl^-** (ppm)[c]	CH_3CN (%)[a]	CH_2Cl_2: CH_3CN (%)[a,b]	**Br^-** (ppm)[c]
Ibu^-	90	100	<6	87	100	<6	61	100	<13

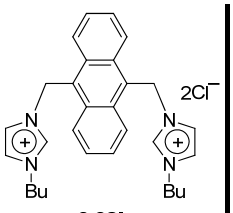
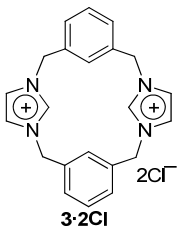
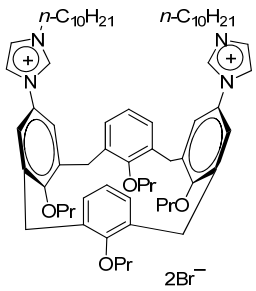
[a]Yield of the recovered new ion pair. [b]CH_3CN:CH_2Cl_2 (3:7). [c]Halide contents after anion exchange determined by silver chromate test; 0.011 mL of $AgNO_3$ aqueous solution is enough to react with nearly 6 ppm ($mg \cdot L^{-1}$) of chloride anion, or 13 ppm ($mg \cdot L^{-1}$) of bromide anion.

Table S4. Comparative results of (anthrylmethyl)imidazolium salt **1·Cl** anion exchange.

 **1·Cl**	CH_3OH (%)[a]	CH_3CN:CH_3OH (%)[a,b]
PF_6^-	70	98
BF_4^-	78	100
$CF_3SO_3^-$	93	95

[a] Yield of the recovered new ion pair. [b]CH_3CN:CH_3OH (9:1).

Table S5. Results of the halide exchange in bis(imidazolium) salts **2·Cl**, **3·2Cl** and **4·Br** in methanol, acetonitrile or solvent mixtures.

compound	 **2·2Cl**		 **3·2Cl**		 **4·2Br**	
Anion	(%)[a]	Cl^- (ppm)[b]	(%)[a]	Cl^- (ppm)[b]	(%)[a]	Br^- (ppm)[b]
AcO^-	70 [100][c]	<6	95	<6	100[d]	<13
BzO^-	100	<6	100	<6	NT	
(*S*)-Lactate$^-$	100	<6	100	<6	NT	
$MeSO_3^-$	42 [100][c]	<6	100	<6	100[d]	<13
$Bu_2PO_4^-$	96	<6	100	<6	98[d]	<13
PF_6^-	32 [95][c]	<6	63 [95][c]	<6	97[d]	<13
BF_4^-	91 [100][c]	<6	100	<6	NT	
$CF_3SO_3^-$	100	<6	100	<6	NT	
NCS^-	95	nd	95	nd	NT	

[a]Yield of the recovered new ion pair. Yields ≥ 95% in CH_3OH were not further investigated. [b]Halide contents after anion exchange determined by silver chromate test; 0.011 mL of $AgNO_3$ aqueous solution is enough to react with nearly 6 ppm ($mg \cdot L^{-1}$) of chloride anion, or 13 ppm ($mg \cdot L^{-1}$) of bromide anion [c]Anion exchange carried out in CH_3CN:CH_3OH (9:1) mixture solution. [d]Anion exchange carried out in CH_3CN.

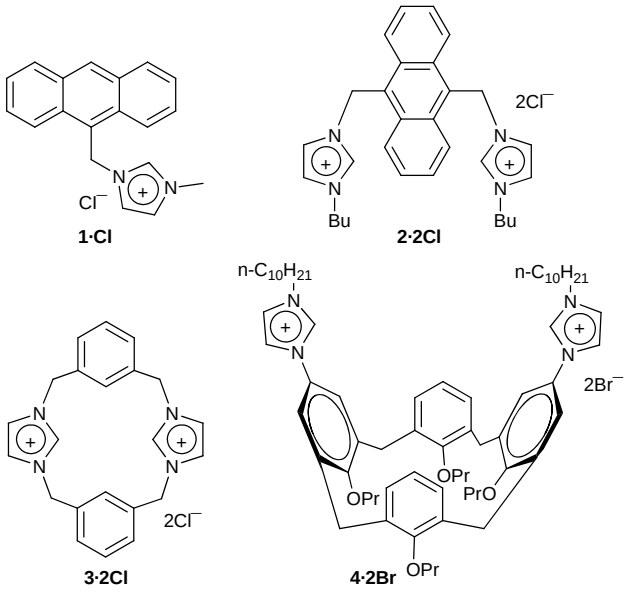


Figure S1 Application of the AER (A^- form) method in organic solvents. In CH_3OH or CH_3CN:CH_3OH [9:1]: (anthrylmethyl)imidazolium salt **1·Cl** was transformed to **1·PF_6^-**, **1·BF_4^-** and **1·$CF_3SO_3^-$**; chloride exchange for a variety of anions from bis(imidazolium)-based anion receptors **2·2Cl** and **3·2Cl** to **2·2A** and **3·2A**, respectively. In CH_3CN: calix[4]arene **4·2Br** to **4·2A**.

EXPERIMENTAL PROCEDURES

General Information

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) and Mercury 400 (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) spectrometers at 298 K. ^{1}H and ^{13}C chemical shifts were referenced with TMS as an internal reference. Mass spectrometric analyses were performed on a LC/MSD-TOF (2006) mass spectrometer with a pumping system HPLC Agilent 1100 from Agilent Technologies at Serveis Científico-Tècnics of Universitat de Barcelona under the following experimental conditions: • Solvent: H_2O:CH_3CN (1:1, v/v) • Gas temperature: 300 ºC • Capillary voltage: 4 KV (positive) and 3.5 KV (negative) • Fragmentor: 75/175 V • Spray gas: N_2 pressure = 15 psi • Drying gas: N_2 flow: 7.0 L·min^{-1} • Flow rate: 200 μL·min^{-1}.

The pH was measured with benchmeter pH1100 (Eutech Instrunments), using Hamilton Flushtrode pH electrode for hydroalcoholic solutions.

Chemical Information

Commercially available products: ion exchanger resin Amberlyst A-26 (Aldrich, OH^- form), glacial acetic acid, benzoic acid, (*S*)-lactic acid (85% solution in water), methanesulfonic acid, dibutylphosphoric acid, hexafluorophosphoric acid solution (65%, gravimetric in water), tetrafuoroboric àcid (50 % in water), Ibuprofen, ammonium acetate, ammonium chloride, ammonium hexafluorophosphate, ammonium thiocyanate, ammonium trifluoromethanesulfonate, ammonium tetrafluoroborate, ammonium tetraphenylborate, 1-bromodecane, [bmim][Cl], [hmim][Cl], [dmim][Cl] and [d_2m_2N][Br]. All solvents were reagent grade and methanol was distilled prior to use. *Compounds prepared according with the literature:* **[bm$_2$im][Br]**,[†] **[bmpy][I]**,[‡] **1·Cl**,[29] **2·2Cl**,[30] **3·2Cl**,[16] and 5,17-bis-(imidazol-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene.[16]

[†] A. K. Burrell, R. E. Del Sesto, S. N. Baker, T. M. McCleskey and G. A. Baker, *Green Chem*., 2007, **9**, 449.
[‡] J. Wang, W.-F. Cao, J.-H. Su, H. Tian, Y.-H. Huang and Z.-R. Sun, *Dyes and Pigments*, 2003, **57**, 171.
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5,17-bis-(3-decyl-1-imidazolium)-25,26,27,28-tetrapropoxycalix[4]arene dibromide 4·2Br

A solution of 5,17-bis-(imidazol-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene (0.300 g, 0.413 mmol) in 1-bromodecane (5 ml) was heated to reflux for 16h, under an argon atmosphere. A light brown solid was collected by filtration and washed with several portions of diethyl ether (3 x 10 mL), obtaining compound **4·2Br** (0.402 g, 83%). m.p. = 268-270 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.28 (s, 2H, Im), 8.20 (s, 2H, Im), 7.27 (d, 4H, $H_{10,12,22,24}$), 7.16 (t, 2H, $H_{11,23}$), 6.68 (s, 2H, Im), 6.53 (s, 4H, $H_{4,6,16,18}$), 4.49-4.54 (m, 8H, H_{ax} and N-C$\underline{H}_2$-), 4.05 (t, 4H, O-C$\underline{H}_2$), 3.70 (t, 4H, O-C$\underline{H}_2$), 3.25 (d, 4H, H_{eq}), 1.87-1.99 (m, 8H), 1.74 (m, 4H), 1.21 (m, 28H), 1.12 (t, 6 H), 0.86 (t, 6 H), 0.91 (t, 6 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 156.9, 137.1, 135.4, 134.0, 129.9, 128.9, 124.8, 124.1, 120.0, 118.9, 77.7, 76.9, 50.4, 31.9, 31.1, 30.7, 29.5, 29.3, 29.2, 26.3, 23.5, 23.0, 22.8, 14.2, 10.8 and 9.9.

Loading the AER (resin (OH^- form) with acids or ammonium salts.

A glass column (1 cm diameter) packed with 2.5 g (~ 3 cm^3) of commercially wet strongly basic anion exchange Amberlyst A-26 (OH^- form) was washed with water, and the column bed was equilibrated progressively with water-solvent mixtures until reaching the selected solvent media used afterwards for anion loading (~ 25 mL of each solvent mixture). A 1% acid or ammonium salt solution in the appropriate solvent was passed slowly through the resin until the eluates had the same pH value as the original selected acid solution, and then the resin was washed generously with solvent until constant pH. The process was carried out at room temperature, using gravity as the driving force.

Anion exchange.

A solution of the imidazolium salt (50-60 mM) in 10 mL of the selected solvent was passed slowly through a column packed with ~ 3 cm^3 of Amberlyst A-26 (A^- form), and then washed with 25 mL of solvent. The combined eluates were evaporated, and the residue obtained was dried in a vacuum oven at 60 ºC with P_2O_5 and KOH pellets.

It should be pointed out that Clare et al. have demonstrated that the use of alumina and silica columns can leave a low level of residual particulate contamination in ILs.[§,9] Consequently, nano-particulates may also be an issue when using strongly basic anion exchange resins (A^- form) but the analysis of possible particulate contamination was out of the scope of the present study.

Silver chromate test

The amount of halide contents was determined by a silver chromate test following a similar protocol to that described by Sheldon and co-workers.[24] An aqueous solution (5 mL) of potassium chromate (5 % p/v in Milli-Q water, 0.257 M) was added to the sample (5-10 mg). To 1 mL of the resulting dark yellow solution was added a silver nitrate aqueous solution (0.24 % p/v in Milli-Q water, 0.014 M). A persistent red suspension of silver chromate would be observed if the sample was free of halide. The minimum measurable amount of silver nitrate aqueous solution was 0.011 mL; consequently, the detection limit is approx. 6 ppm for Cl^-, 13 ppm for Br^- or 20 ppm for I^-. The halide content was determined at least twice for each sample.

§ B. R. Clare, P. M. Bayley, A. S. Best, M. Forsyth and D. R. MacFarlane, *Chem. Commun.*, 2008, 2689.

9. B. Clare, A. Sirwardana and D. R. MacFarlane, *Top. Curr. Chem.*, 2009, **290**, 1.

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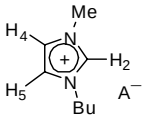
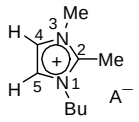
Table S6. ^{1}H NMR chemical shift values of 1-butyl-3-methylimidazolium salts **[bmim][A]** in $CDCl_3$ (300 MHz) at 298 K.[a]



Anion	H-2	H-4	H-5	Bu	Me	A^-
BzO^-	11.54	7.09	7.09	4.29; 1.84; 1.33; 0.92	4.08	8.10; 7.33
Ph_4B^-	4.52	5.95	5.77	3.13; 1.32; 1.12; 0.89	2.73	7.52; 6.92; 6.78
Ph_4B^-[b]	8.29	7.33	7.29[c]	4.09; 1.79; 1.33; 0.94	3.78	7.29; 6.99; 6.84
Ph_4B^-[d]	9.06	7.74	7.68	4.14; 1.75; 1.27; 0.90	2.07	7.18; 6.93; 6.79
Ibu^-	9.86	7.10	7.02	4.02; 1.66; 1.24; 0.87	3.71	7.26; 6.95; 3.53; 2.35; 1.75; 1.39; 0.82

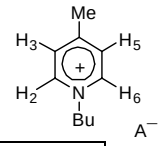
[a]Solution concentrations are 0.02 M. [b]In CD_3CN.[c]Included in the Ph signal. [d]In DMSO-d_6.

Table S7. ^{1}H NMR chemical shift values of 1-butyl-2,3-dimethylimidazolium salts **[bm$_2$im][A]** in $CDCl_3$ (300 MHz) at 298 K.[a]



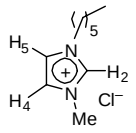
Anion	H-4	H-5	Me-2	Me-3	Bu	A^-
AcO^-	7.58	7.36	2.59	3.82	4.06; 1.67; 1.26; 0.86	1.72
BzO^-	7.54	7.27	2.50	3.71	3.90; 1.58; 1.23; 0.85	7.97; 7.27
(S)-$Lactate^-$	7.49	7.26	2.70	3.92	4.12; 1.79; 1.40; 0.98	3.87; 1.30
$MeSO_3^-$	7.47	7.27	2.69	3.94	4.14; 1.80; 1.38; 0.98	2.74
$Bu_2PO_4^-$	7.55	7.27	2.68	3.92	4.13; 1.76; 1.37; 0.96	3.77; 1.56; 1.37; 0.89
PF_6^-	7.46	7.30	2.70	3.90	4.11; 1.79; 1.40; 0.96	
BF_4^-	7.40	7.27	2.68	3.88	4.10; 1.79; 1.40; 0.97	
$CF_3SO_3^-$	7.32	7.22	2.66	3.86	4.09; 1.80; 1.40; 0.97	
NCS^-	7.43	7.32	2.77	3.96	4.17; 1.83; 1.43; 0.98	

Table S8. ^{1}H NMR chemical shift values of 1-butyl-4-methylpyridinium salts **[bmpy][A]** in $CDCl_3$ (300 MHz) at 298 K.

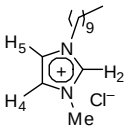


Anion	**H-2,6**	**H-3,5**	**Me**	**Bu**	**A$^-$**
AcO^-	9.35	7.82	2.62	4.82; 1.96; 1.35; 0.94	1.96
BzO^-	8.94	7.70	2.47	4.67; 1.82; 1.25; 0.83	8.00; 7.31
(S)-Lactate$^-$	9.05	7.81	2.57	4.65; 1.88; 1.35; 0.87	3.89; 1.26
$MeSO_3^-$	9.09	7.83	2.57	4.65; 1.91; 1.32; 0.87	2.68
$Bu_2PO_4^-$	9.36	7.83	2.53	4.72; 1.89; 1.30; 0.83	3.78; 1.50; 1.30; 0.83
PF_6^-	8.60	7.80	2.66	4.54; 1.95; 1.39; 0.95	
BF_4^-	8.73	7.82	2.66	4.60; 1.95; 1.39; 0.95	
$CF_3SO_3^-$	8.80	7.82	2.65	4.60; 1.94; 1.38; 0.94	
NCS^-	8.94	7.91	2.70	4.77; 2.03; 1.44; 0.99	

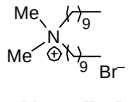
Table S9. ^{1}H NMR chemical shift values of imidazolium salts **[hmim][A]** and **[dmim][A]**, and quaternary ammonium salt **[d$_2$m$_2$N][A]** in $CDCl_3$ (300 MHz) at 298 K.



[hmim][Cl]



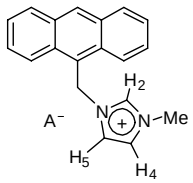
[dmim][Cl]



[d$_2$m$_2$N][Br]

Cation	**Anion**	**H-2**	**H-4**	**H-5**	**C_nH_{n+1}**	**Me**	**A$^-$**
[hmim]	[Cl^-]	10.80	7.44	7.31	4.30; 1.89; 1.30; 0.86	4.11	–
	[Ibu^-]	9.72	7.08	7.01	4.05; 1.74; 1.26; 0.86	3.75	7.28; 7.01; 3.54; 2.37; 1.78; 1.41; 0.86
[dmim]	[Cl^-]	10.82	7.38	7.27	4.32; 1.89; 1.27; 0.86	4.12	–
	[Ibu^-]	10.58	7.01	6.99	4.11; 1.78; 1.25; 0.87	3.81	7.31; 6.98; 3.60; 2.39; 1.79; 1.46; 0.87
[d_2m_2N]	[Br^-]				3.51; 1.65; 1.30; 0.88	3.41	–
	[Ibu^-]				3.10; 1.52; 1.26; 0.88	3.01	7.30; 7.00; 3.57; 2.39; 1.81; 1.42; 0.88

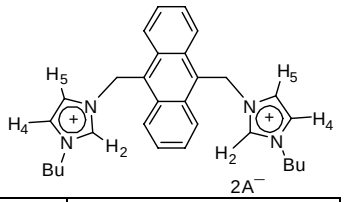
Table S10. ^{1}H NMR chemical shift values of 1-[(9-antryl)methyl]-3-methylimidazolium salts **1·A** in CD_3CN (300 MHz) at 298 K.



Anion	H-2	H-4	H-5	Antryl	–CH_2–	Me	A^-
Cl^-	8.73	7.38	7.30	8.77; 8.36; 8.18; 7.63	6.42	3.70	
PF_6^-	8.13	7.35	7.28	8.72; 8.24; 8.15; 7.62	6.26	3.65	
BF_4^-	8.16	7.33	7.29	8.71; 8.23; 8.14; 7.61	6.27	3.66	
TfO^-	8.09	7.40	7.29	8.79; 8.26; 8.20; 7.64	6.31	3.65	
BPh_4^-	8.10	7.36	7.30	8.79; 8.25; 8.20; 7.64	6.29	3.62	7.28; 6.99; 6.84
BPh_4^{-b}	8.80	7.18	7.18	8.85; 8.8.45; 8.22; 7.68	6.47	3.72	7.18; 6.92; 6.78

[a]Solution concentrations are 0.02 M. [b]In DMSO-d_6

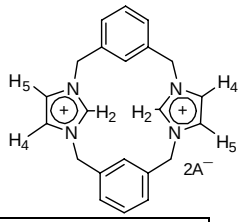
Table S11. ^{1}H NMR chemical shift values of 9,10-bis[(3-butyl-1-imidazolio)methyl]anthracene **2·2A** in $CDCl_3$ (300 MHz) at 298 K.



Anion	H-2	H-4	H-5	Ar	–CH_2–	Bu	A^-
AcO^{-a}	10.04	7.71	7.64	8.74; 7.99	6.78	4.37; 2.00; 1.50; 1.14	1.94
BzO^{-b}	c	7.63	7.52	8.52; 7.93	6.58	4.10; 1.75; 1.26; 0.89	7.77; 7.34
(S)-Lactate$^-$	10.26	7.07	7.07	8.13; 7.46	6.44	4.07; 1.70; 1.20; 0.83	3.87; 1.25
$MeSO_3^-$	9.15	7.74	7.13	7.88; 7.33	6.28	4.03; 1.62; 1.14; 0.76	2.44
$Bu_2PO_4^-$	10.20	7.33	7.15	8.03; 7.35	6.44	4.06; 1.69; 1.18; 0.83	3.72; 1.51; 1.31; 0.83
PF_6^-	9.29	8.27	7.04	7.79; 7.30	6.38	4.03; 1.60; 1.14; 0.78	
BF_4^-	9.03	8.38	7.08	7.79; 7.24	6.36	4.01; 1.58; 1.12; 0.76	
$CF_3SO_3^{-a}$	c	8.40	8.40	7.74; 7.37	6.40	4.02; 1.71; 1.23; 0.85	
NCS^-	8.70	8.18	7.22	7.89; 7.41	6.33	4.01; 1.65; 1.20; 0.80	

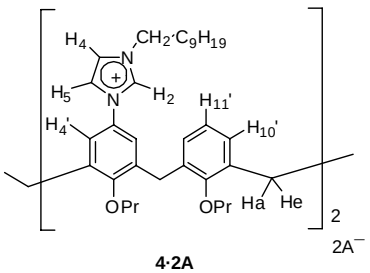
[a]In CD_3CN. [b]In CD_3OD. [c]Signal not observed.

Table S12. ^{1}H NMR chemical shift values of bis(imidazolium) heterophane **3·2A** in DMSO-d_6 (300 MHz) at 298 K.



Anion	H-2	H-4,5	–CH_2–	Ph	A^-
AcO^-	10.77	7.82	5.42	7.81; 7.59; 7.40	1.68
BzO^-	10.70	7.80	5.43	7.80; 7.59; 7.40	7.93; 7.28
(S)-$Lactate^-$	9.91	7.79	5.42	7.79; 7.58; 7.49	3.50; 1.35
$MeSO_3^-$	9.34	7.81	5.43	7.81; 7.59; 7.48	2.31
$Bu_2PO_4^-$	10.49	7.77	5.41	7.73; 7.59; 7.42	3.63; 1.44; 1.29; 0.83
PF_6^-	8.20	7.75	5.39	7.75; 7.54; 7.38	
BF_4^-	9.68	7.82	5.43	7.59; 7.49; 7.33	
$CF_3SO_3^-$	9.23	7.82	5.43	7.57; 7.51; 6.93	
NCS^-	9.23	7.82	5.43	7.82; 7.56; 6.94	

Table S13. ^{1}H NMR chemical shift values of bis(imidazolium)calixarene **4·2A** in $CDCl_3$ (300 MHz) at 298 K.[a]



4·2A

Anion	H_2	H_4	H_5	$H_{10'}$	$H_{11'}$	$H_{4'}$	N-CH_2-	H_a	H_e	A^-
Br^-	9.28	8.20	6.68	7.27	7.16	6.53	4.51	4.52	3.25	
AcO^-	9.87	7.71	7.05	7.25	7.05	6.46	4.20	4.48	3.25	1.95
$MeSO_3^-$	9.07	7.70	6.83	7.26	7.06	6.47	4.31	4.50	3.25	2.80
$Bu_2PO_4^-$	9.74	8.00	6.90	7.27	7.07	6.43	4.27	4.47	3.25	3.86; 1.60; 1.38; 0.86
PF_6^-[b]	8.72	6.61	6.59	7.45	6.51	7.14	4.17	4.54	3.31	
PF_6^-[c]	9.79	8.26	8.01	6.36	6.36	7.59	4.23	4.43	3.30	

[a]Solution concentrations are 0.02 M. [b]In CD_3CN. [c]In DMSO-d_6.

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  Molecules, **2012**, *17(4)*, 4007-4027.

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Article

A Simple Halide-to-Anion Exchange Method for Heteroaromatic Salts and Ionic Liquids

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Abstract: A broad and simple method permitted halide ions in quaternary heteroaromatic and ammonium salts to be exchanged for a variety of anions using an anion exchange resin (A^- form) in non-aqueous media. The anion loading of the AER (OH^- form) was examined using two different anion sources, acids or ammonium salts, and changing the polarity of the solvents. The AER (A^- form) method in organic solvents was then applied to several quaternary heteroaromatic salts and ILs, and the anion exchange proceeded in excellent to quantitative yields, concomitantly removing halide impurities. Relying on the hydrophobicity of the targeted ion pair for the counteranion swap, organic solvents with variable polarity were used, such as CH_3OH, CH_3CN and the dipolar nonhydroxylic solvent mixture CH_3CN:CH_2Cl_2 (3:7) and the anion exchange was equally successful with both lipophilic cations and anions.

Keywords: imidazolium salts; pyridinium salts; ammonium salts; anion exchange resin; counteranion exchange; ionic liquids

1. Introduction

Besides their recognized value as an alternative to conventional solvents, ionic liquids (ILs) are becoming increasingly useful in a widening range of fields in chemistry leaning toward biology. Indeed, ILs have featured extensively in recent scientific open literature and patents, which reflects their importance in research and development (R&D) [1–9]. The greenness of commonly used IL

syntheses and purification procedures has been analyzed and evaluated [10] as well as their environmental acceptability and their role in sustainable development [11]. Simple imidazolium quaternary salts with a low melting point are a long-standing IL family and at the same time imidazolium-based systems have continued their progress in anion recognition chemistry and *N*-heterocyclic carbenes (NHCs) [12].

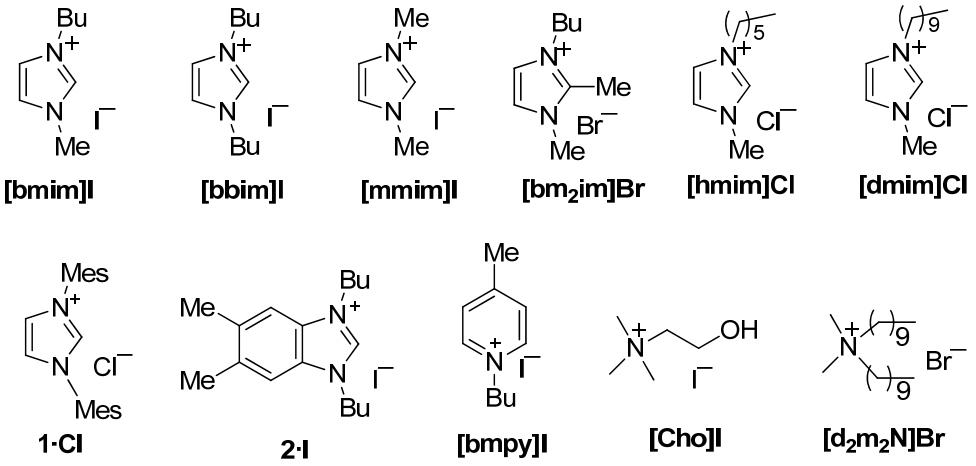
Chemical aspects of imidazolium-based ILs dealing with their preparation, counteranion exchange and purity have been the subject of numerous studies and are currently being investigated with the aim of obtaining pure IL salts, especially halide-free ion pair compounds [4,10,12–16]. A widespread synthesis of imidazolium ILs makes use of a subclass of the Menschutkin reaction, a nucleophilic substitution carried out under neutral conditions between *N*-substituted imidazoles and an alkyl or benzylhalides, affording the targeted imidazolium system in which the counteranion, that is, the halide ion, can be exchanged by different methods. The most frequent method is the classical halide ion exchange with an inorganic salt (MA) that is also used to remove halide ions in ILs. The halide-containing byproduct salts can then be removed by extraction or precipitation followed by filtration. The challenging issue of purification can be addressed by several IL clean-up protocols to eliminate the unwanted halide and/or metal species, among other byproducts [13–16]. The isolation and purification of pure heteroaromatic quaternary systems can be troublesome, especially if the different ionic species present in the solution-phase have a similar solubility. In this context, a comparative study of the transformation of *N*-azolylpyridinium salts to the corresponding pyridinium azolate betaines showed that the method of choice makes use of a strongly basic anion exchange resin, AER (OH^- form) [17]. From 1986 onwards, the AER (OH^- form) method has been applied to a variety of *N*-azolylimidazolium and *N*-azolylpyridinium salts with several interanular linkers. Exploiting our standard AER (OH^- form) method, the halide-to-anion exchange of different types of bis(imidazolium) cyclophanes, protophanes and calix[4]arenes was carried out using a column chromatography packed with a strongly basic AER (OH^- form) followed by immediate collection of the eluates in diluted aqueous acid solution [12,18–22].

The few examples of anion exchange resin application to ILs reported in the open literature use: (a) the AER (OH^- form) method, involving the swap of halides for OH^-, and then to the **[IL][OH]** aqueous or hydroalcoholic solution was slowly added a slight excess of an aqueous acid solution and displacement of the OH^- anion by the selected A^- anion; or (b) the AER (A^- form) method, involving the incorporation of the anion in the resin (OH^- form) before the anion is exchanged in ILs. Taking advantage of the AER (OH^- form) method, Ohno and co-workers prepared Bio-ILs using strong basic Amberlite (OH^- form) to exchange a halide ion for OH^-, and organic acids or natural aminoacids were added to the aqueous solution of **[IL][OH]** to prepare examples of imidazolium-based **[IL][A]** [23,24]. Choline cations were similarly transformed to the corresponding ionic liquids [25]. In the same way, several ionic liquid buffers were prepared by treatment of the aqueous solution of **[IL][OH]** with organic acids [26]. There are only a few reports exploiting the AER (A^- form) method in water or aqueous methanol. Thus, several examples of non-aqueous ionic liquids (NAILs) have been prepared using an AER (PO_4^{3-} form) [27]. An AER (OH^- form) was loaded with mesylate or tosylate anions by treatment with the corresponding sulfonic acid and the prepared AER (R/Ar-SO_3^- form) was then used to transform several *N*,*N*'-dialkylpyrrolidinium iodides to the corresponding sulfonate cations [28]. Loading the anion exchanger with camphorsulfonate anion, AER (CS^- form) gave the corresponding **[IL][CS]**from either **[IL][OTs]** [29] or **[IL]Br** [30], the latter following a worthless protocol.

Treatment of **[bmim]Cl** with the AER (A^- form) -acetate, lactate and nitrate- produced the anion exchange giving **[bmim][A]** [31]. Recently, we examined the preparation of an AER (A^- form) conveniently loaded with a selected anion by treatment with either acids or ammonium salts in water or hydroalcoholic media. The anion exchange was carried out in methanol, providing a pure ionic liquid in quantitative yield. This simple procedure not only offers a convenient way to replace halide anions by a broad range of anions in ILs, including task-specific and chiral ILs, but also eliminates halide impurities [32]. Further studies have been directed towards expanding the scope of the halide-for-anion swap in non-aqueous media to representative imidazolium ILs and known examples of bis(imidazolium)-based frameworks for anion recognition. Both lipophylic imidazolium systems and low hydrophilic anions proceeded in excellent to quantitative yields [33].

In this paper we report how the AER (A^- form) method can be exploited for a halide-to-anion exchange in several illustrative examples from IL families. The anion source and solvent selection for loading the AER (OH^- form) were first examined using different acids or ammonium salts and organic solvent mixtures with variable polarity. The halide-to-anion exchange was then studied using imidazolium-based ILs, random examples of quaternary azolium and pyridinium salts as well as quaternary ammonium salts from the APIs family (Figure 1).

Figure 1. The AER (A^- form) method applied to representative quaternary heteroaromatic salts and quaternary ammonium salts.



2. Results and Discussion

2.1. AER (A^- Form) Method. Anion Loading

Anion source. Two methods were used to load the anions: Via *A*, from acids, or via *B*, involving the corresponding ammonium salt (Scheme 1 and Table 1).

The AER (OH^- form) was packed in a column and treated with an aqueous or hydromethanolic solution of the acid or ammonium salt. The loading effectiveness was then checked by passing a methanolic solution of **[bmim]I** through the AER column loaded with the target anion and the halide ion to another anion exchange proceeded in quantitative yield.

Scheme 1. AER (A^- form) method: The loading.

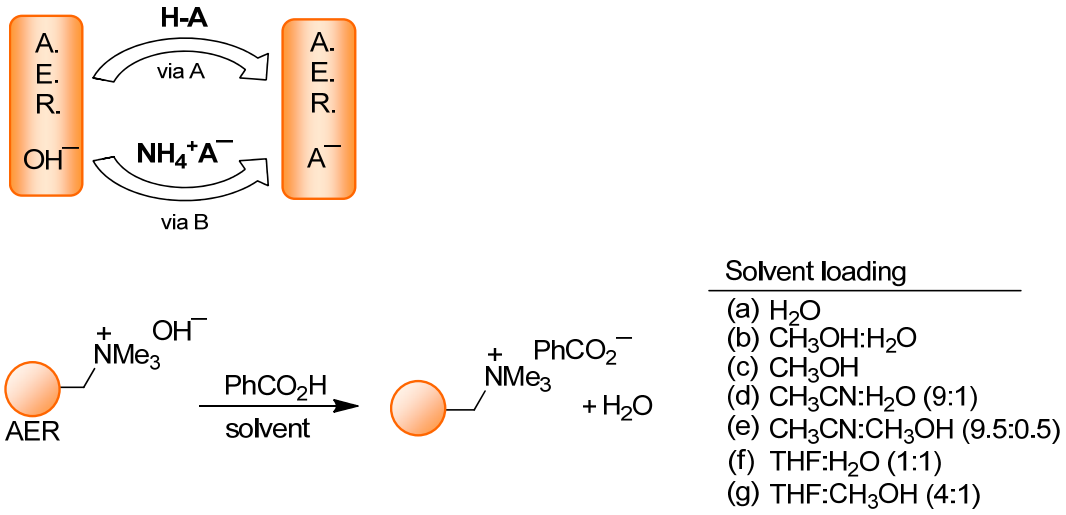


Table 1. Loading AER (OH^- form): Anion source and solvents.

Anion	Source	Solvent	Anion	Source	Solvent
AcO^-	$NH_4^+AcO^-$	(a)	AcO^-	AcOH	(b)
Cl^-	$NH_4^+Cl^-$	(a)	Cl^-	HCl	(a), (b)
PF_6^-	$NH_4^+PF_6^-$	(a)	PF_6^-	HPF_6	(b)
BF_4^-	$NH_4^+BF_4^-$	(a)	BF_4^-	HBF_4	(b)
$CF_3SO_3^-$	$NH_4^+CF_3SO_3^-$	(a)	BzO^-	BzOH	(b)–(g)
SCN^-	NH_4^+ SCN^-	(a)	(*S*)-Lactate$^-$	(*S*)-Lactic acid	(b)
F^-	$NH_4^+F^-$	(a)	$MeSO_3^-$	$MeSO_3H$	(b)
$H_2PO_4^-$	$NH_4^+H_2PO_4^-$	(a)	$Bu_2PO_4^-$	Bu_2PO_4H	(b), (c)
HSO_4^-	$NH_4^+HSO_4^-$	(a)	ClO_4^-	$HClO_4$	(a), (b)
Ph_4B^-	$NH_4^+Ph_4B^-$	(d), (e)	NO_3^-	HNO_3	(a), (b)
			Ibu$^-$	Ibuprofene	(d), (e)

Solvent: (a) H_2O; (b) CH_3OH:H_2O; (c) CH_3OH; (d) CH_3CN:H_2O (9:1); (e) CH_3CN:CH_3OH (9.5:0.5); (f) THF:H_2O (1:1); (g) THF:CH_3OH (4:1).

Thus, following via *A*, the resin was charged with organic oxoanions derived from carboxylate ($R\text{-}CO_2^-$), including chiral (*S*)-lactate, sulfonate ($MeSO_3^-$) or phosphate ($Bu_2PO_4^-$), together with inorganic anions such as Cl^-, NO_3^- or ClO_4^-, by treatment with the corresponding 1% aqueous acidic solutions. When the loading was performed with the aqueous solution of CF_3SO_3H, HF, H_3PO_4 or H_2SO_4, the polymeric matrix was partially denaturalized by overheating. For this reason, anions such as $CF_3SO_3^-$, F^-, $H_2PO_4^-$ or HSO_4^- were loaded in the resin using aqueous solutions of their ammonium salts (via *B*). In order to confirm the efficiency of the method, both procedures were used to load AcO^-, Cl^-, PF_6^- or BF_4^- anions, and identical results were obtained. A few attempts to load anions from their corresponding Na^+, K^+ or Li^+ salt showed, however, that the replacement of OH^- in the AER was incomplete, as evidenced by an observed mixture of anions in the checking, and this was not further studied.

Solvent selection. We extended our studies to the loading of hydrophobic anions, and explored alternative solvents and solvent mixtures. Benzoic acid was selected to prepare the AER (BzO^- from)

and then a methanolic solution of **[bmim]I** was used to check the iodide-to-benzoate anion switch. The resin was first packed in a column and generously washed with the solvent, which was used afterwards to load the benzoate anion. Pure solvents such as distilled CH_3OH, CH_3CN, THF and CH_2Cl_2 were assayed, but only CH_3OH provided the optimal loading. Then, several solvent mixtures containing CH_3CN or THF with H_2O or CH_3OH were applied. Among the successful loading solvent mixtures that provided the AER in the BzO^- form, those with the lowest proportions of water or methanol were CH_3CN:H_2O (9:1), CH_3CN:CH_3OH (9.5:0.5), THF:H_2O (1:1) or THF:CH_3OH (4:1) (Scheme 1 and Table 1).

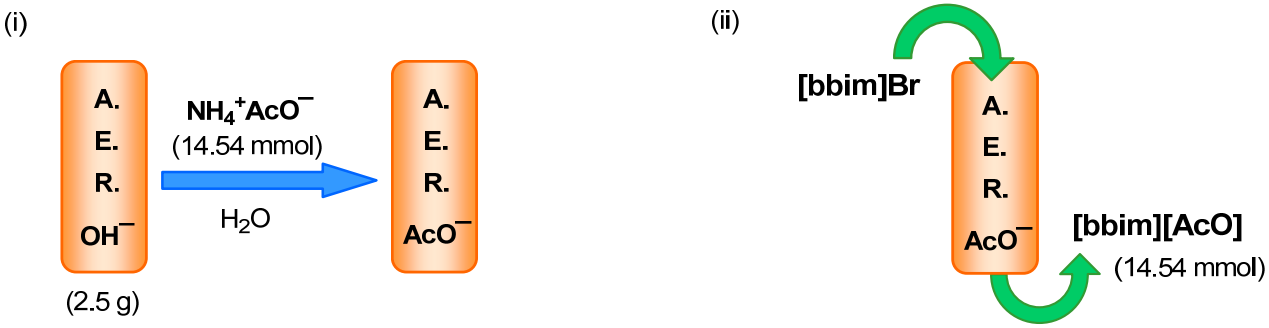
These results indicated that a non-aqueous mixture can be used to incorporate lipophylic anions, although the presence of a protic solvent was necessary for the OH^- replacement in the AER. Once the suitable solvent conditions were found, acetonitrile solvent mixtures were used to load representative hydrophobic anions: The anti-inflammatory acid ibuprofen to explore via A and ammonium tetraphenylborate to explore via B.

In order to check the loading effectiveness, a methanolic solution of **[bmim]I** was passed through the AER (Ibu^- form) or AER (Ph_4B^- form) and the pure **[bmim][Ibu]** [34] or **[bmim][Ph_4B]** [35] was obtained (see later). These results confirmed that lipophylic anions replace the OH^- anion in resin when using the appropriate solvent and the corresponding AER (A^- form) obtained can then be used for the halide-to-anion switch.

Loading and exchange ability. The anion amount that the AER can load and the amount of halide that can then be exchanged were examined. Thus, 2.5 g (~3 cm^3) of commercial wet A-26 (OH form) was treated with a 1% NH_4AcO aqueous solution until the pH value of the eluates indicated that loading was complete. Thus, 14.54 mmol of AcO^- was loaded with a maximum loading of 5.8 mmol of AcO^- per 1 g of this AER. In this context, the synthesis and characterization of resin-supported organotrifluoroborates have recently been reported and the loading was quantified by a UV/Vis spectroscopic analysis [36].

A 50 mM methanolic solution of **[bbim]Br** was passed through the packed column and aliquots were collected periodically and examined by ^{1}H-NMR. The related integration of signals corresponding to the anion and imidazolium cation indicated that the exchange process was quantitative up to nearly 14.54 mmol of ionic liquid, suggesting that the Br^- exchange could take place as long as there was enough AcO^- anion (Scheme 2).

Scheme 2. AER (A^- form) method. (**i**) Maximum anion loading. (**ii**) Checking anion exchange capacity.



Additionally, it should also be considered that the AER used in the exchange can be recycled by treatment with 10% NaOH aqueous solution, and the recovered AER (OH^- form) can be re-utilized for a new anion loading. In the present study, the chosen resin was Amberlyst A-26, given that it allows the use of aqueous mixtures and non-aqueous solvents, but other similar strongly basic anion exchange resins can be used instead.

2.2. AER (A^- Form) Method. Anion Exchange

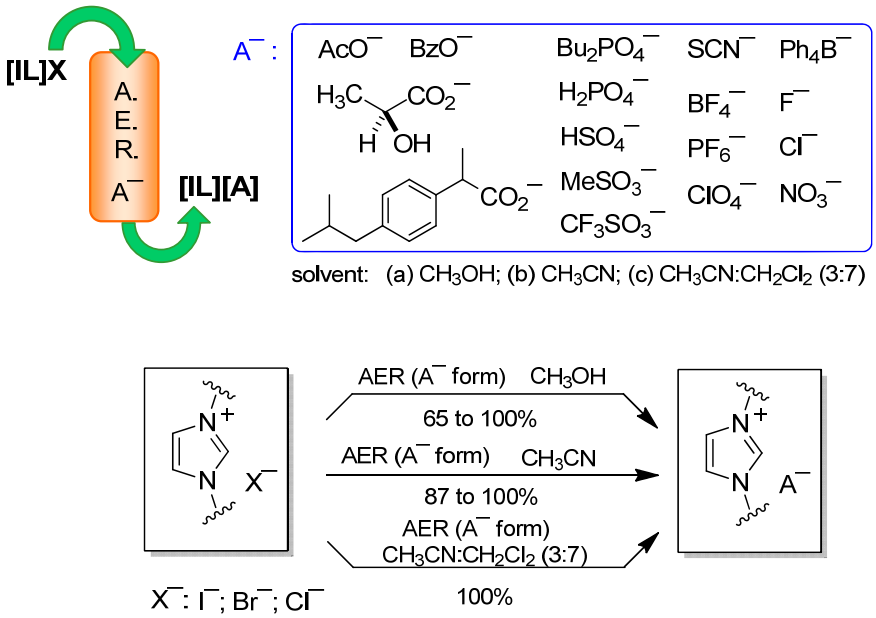
Having achieved the loading of several anions in the AER, we examined their efficiency in the counterion exchange in imidazolium-based ILs, including **[bmim]I** or **Br**, **[bbim]I** or **Br** or **[mmim]I** as well as **[bm$_2$im]Br**. Thus, a methanolic solution of IL was passed through a column packed with the AER (A^- form) previously prepared, and the solvent was removed from the collected eluates. Following this simple method, in almost all cases I^- or $Br^- \geq 95\%$ halide-for-anion swapping was obtained except for the hydrophobic anions Ph_4B^- and Ibu^-, which gave for example, from **[bmim]I** in 65% and 95% yield, respectively (Table 2 and Scheme 3).

Table 2. Results of the iodide or bromide exchange in imidazolium ionic liquids.

		[bmim]I or **Br**		**[bbim]I** or **Br**		**[mmim]I**		**[bm$_2$im]Br**	
Anion	**Solvent**	**Yield (%)** [a]	**I^- (ppm)** [b]	**Yield (%)** [a]	**I^- (ppm)** [b]	**Yield (%)** [a]	**I^- (ppm)** [b]	**Yield (%)** [a]	**Br^- (ppm)** [b]
AcO^-	CH_3OH	100	<20	100	<20	100	<20	98	<13
BzO^-	CH_3OH	100	<20	100	<20	95	<20	100	<13
(*S*)-Lactate$^-$	CH_3OH	100	20–40	100	<20	100	<20	100	<13
$MeSO_3^-$	CH_3OH	100	<20	100	<20	95	<20	92	<13
$MeSO_3^-$	CH_3CN	—		—		—		100	<13
$Bu_2PO_4^-$	CH_3OH	100	<20	100	<20	100	<20	100	<13
F^-	CH_3OH	82	ND [c]	100	ND [c]	—		—	
Cl^-	CH_3OH	100	ND	100	ND	100	ND	—	
PF_6^-	CH_3OH	100	20–40	100	<20	100	<20	91	ND
PF_6^-	CH_3CN	—		—		—		100	13–26
NO_3^-	CH_3OH	100	<20	100	<20	100	20–40	—	
ClO_4^-	CH_3OH	100	100–120	100	20–40	100	20–40	—	
BF_4^-	CH_3OH	100	<20	100	<20	100	20–40	97	13–26
$H_2PO_4^-$	CH_3OH	100	<20	100	20–40	100	<20	—	
HSO_4^-	CH_3OH	100	<20	100	20–40	100	<20	—	
$CF_3SO_3^-$	CH_3OH	100	<20	100	<20	100	<20	100	<13
SCN^-	CH_3OH	100	ND	100	ND	100	ND	100	ND
Ph_4B^-	CH_3OH	65	<20	45	<20	—		—	
Ph_4B^-	CH_3CN	95	<20	100	<20	—		91	<13
Ibu^-	CH_3OH	95	<20	—		—		—	
Ibu^-	CH_3CN	100	<20	—		—		96	<13

ND: Not Determined. [a] Recovered new ion pair. Yields ≥95% in CH_3OH were not further examined in CH_3CN; [b] Halide contents after anion exchange determined by the silver chromate test; [c] Analyzed by HPLC/IC from exchange of Br^- by F^-: Presence of Br^- anion was not observed.

Scheme 3. AER (A^- form) method applied to imidazolium-based ILs.



Moreover, no evidence of *N*-heterocyclic carbenes (NHCs) and/or dealkylation by-product formation was observed despite the basic environment, e.g., anion basicity [13,37,38]. The purity of the ionic liquids obtained by this method was qualitatively determined using ^{1}H-NMR spectra, and/or ESI(−)-MS experiments, and according to the silver chromate test, most analyses indicated low halide contents (<20 ppm for I^- or <13 ppm for Br^-). Further quantification of possible halide impurity was restricted by instrumental limitation [32].

Although the halide exchange occurred with lipophylic anions such as Ph_4B^-, when the process was carried out in methanol the yield of the recovered compound decreased to 65%, due to the change of solubility of the new ion pair, which caused their partial retention in the resin. Hence, organic solvents such as CH_3CN or CH_2Cl_2 or CH_3CN:CH_2Cl_2 solvent mixtures were then selected to perform the halide switch, the treatment of **[bmim]I** with AER (BzO^- form) being used to check the process. The results indicated that the exchange was successful in both aprotic organic solvents, while the use of pure CH_2Cl_2 as a solvent in our usual exchange procedure was discarded due to experimental difficulties, after testing several combinations, the mixture with the highest proportion of dichloromethane that was workable was found to be CH_3CN:CH_2Cl_2 (3:7). This enabled a quantitative iodide-for-benzoate swap and afforded the possibility for those exchanges of hydrophobic ionic species.

Accordingly, the preparation of **[bmim][Ph_4B]** or **[bbim][Ph_4B]** from their corresponding iodide salts using the AER (Ph_4B^- form) in CH_3OH provided the corresponding ion pair in 65% and 45% yield, respectively. The yield increased to 95% and 100% when CH_3CN was used, confirming that less polar solvents in the exchange process substantially improved the recovery of the less hydrophilic ion pair (Scheme 4). Similarly, **[bm_2im]Br** was directly studied in CH_3CN and the exchange of Ph_4B^- and Ibu^- anions proceeded in 91% and 96% yields, respectively (Table 2).

Hydrophobic salts such as hexylmethylimidazolium chloride **[hmim]Cl** or decylmethylimidazolium chloride **[dmim]Cl** were used to swap the chloride for the ibuprofenate anion. A solution of the corresponding ionic liquid in CH_3CN was passed through the AER (Ibu^- form) affording the anion exchange in ≤95% yields. A more lipophylic solvent was then used and quantitative results were

obtained with the dipolar nonhydroxylic organic solvent mixture CH_3CN:CH_2Cl_2 (3:7) (Scheme 4 and Table 3).

Scheme 4. AER (A^- form) method. Halide to lipophylic anion exchange.

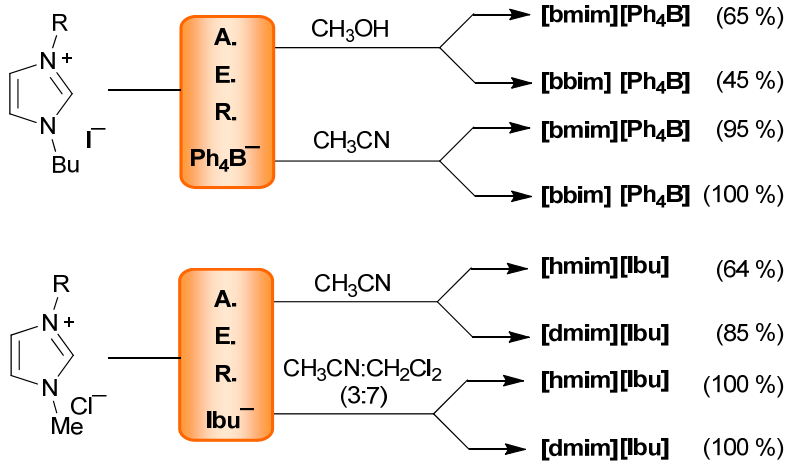


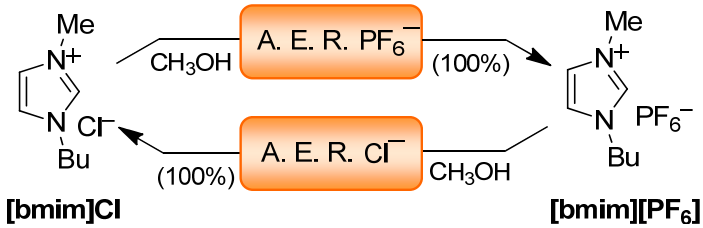
Table 3. Comparative results of chloride exchange in **[hmim]Cl** and **[dmim]Cl**.

Cation	Anion	Solvent	Yield (%) [a]	Cl^- (ppm) [b]
hmim	Ibu^-	CH_3CN	90	<6
	Ibu^-	CH_3CN:CH_2Cl_2 (3:7)	100	<6
dmim	Ibu^-	CH_3CN	87	<6
	Ibu^-	CH_3CN:CH_2Cl_2 (3:7)	100	<6

[a] Yield of the recovered new ion pair; [b] Halide contents after anion exchange determined by silver chromate test.

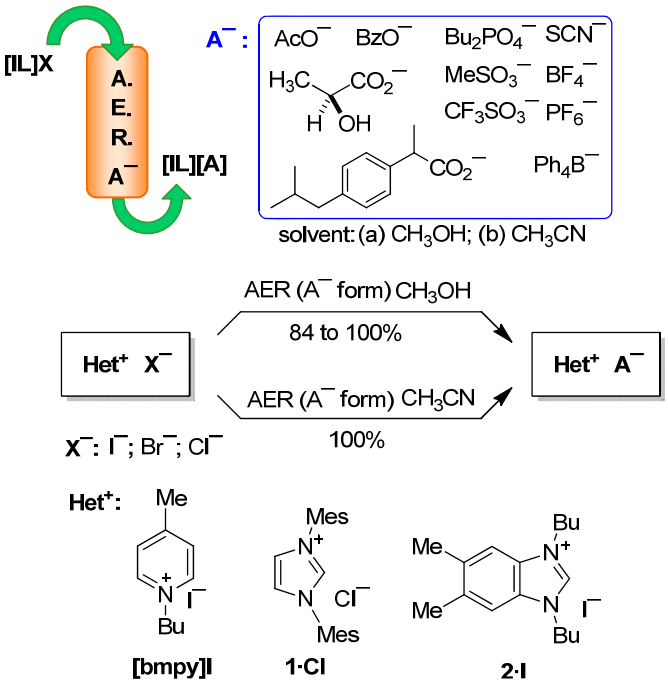
Next, the AER (A^- form) method was extended to other anions. Thus, a methanolic solution of **[bmim]Cl** was passed through the AER (PF_6^- form) packed column and the eluates were analyzed after the solvent was removed. The ^{1}H-NMR spectrum coincided with that of **[bmim][PF_6]**, which indicated a successful exchange confirmed by the silver chromate test (<6 ppm of Cl^-). Similarly, a methanolic solution of **[bmim][PF_6]** was passed through the AER (Cl^- form) packed column and the ^{1}H-NMR spectrum also showed the quantitative exchange (Scheme 5). Thus, a conveniently loaded AER can be used to carry out the swapping from a range of anions other than halides. The process was followed by ^{1}H-NMR, since the signal corresponding to the C(2)-H of the imidazolium moiety is generally the most influenced by the nature of the anion (see Experimental section); for example, the chemical shift value measured in $CDCl_3$ (0.02 M) is 9.07 ppm in **[bmim][PF_6]** while in the same conditions this value is 10.99 ppm in **[bmim]Cl**.

Scheme 5. AER (A^- form) method: Chloride to hexafluorophosphate exchange and vice versa.



Regarding other heteroaromatic cationic systems, pyridinium (**[bmpy]I**) or benzimidazolium (**2·I**) nuclei were chosen as examples to carry out the anion swap, together with the well known NHC precursor 1,3-dimesitylimidazolium salt (**1·Cl**) (Figure 1 and Scheme 6). A methanolic solution of **[bmpy]I** was passed through a column packed with the convenient AER (A^- form), and the corresponding pure **[bmpy][A]** were obtained in ≥ 98% yield, except for the acetate anion, which was recovered in 84% yield. Changing to a more hydrophobic solvent, the iodide-for-acetate swap in acetonitrile proceeded in quantitative yield. In the treatment of **[bmpy]I** with the AER (A^- form), there was no evidence in any case of the formation of decomposition byproducts, despite the basicity of some anions, e.g., acetate (Table 4).

Scheme 6. Halide-to-anion exchange in quaternary azolium and pyridinium salts.



Following the same procedure, a methanolic solution of the new benzimidazolium salt **2·I** was used to obtain the corresponding ion pair **2·A**, with excellent yields. The iodide exchange of the white solid **2·I** (m.p. 150–1 °C) led to oily ion pairs at room temperature or solids with a low melting point (see Experimental section). The new benzimidazolium salts **2·A** are related to previously reported benzimidazolium salts with potential use as new materials, e.g., ionic liquid crystals [39] and crystalline metal-containing ILs [40–42]. Likewise, the chloride anion in 1,3-dimesitylimidazolium salt **1·Cl** can be successfully displaced by a wide range of anions using the AER (A^- form). When the swapping took place in methanol, the recovery of **1·A** was between 80 to 95%, but in acetonitrile yields were nearly quantitative (Table 4). In all cases the silver chromate test revealed the low chloride content after the exchange (<6 ppm), which confirmed the easy swapping of Cl^- anion. These examples demonstrated that the method is also effective with non IL cationic systems, and is a general method for preparing tuneable quaternary heteroaromatic salts. Accordingly, the well-known catalyst precursor **1·Cl** [43] was easily transformed in **1·A**, and the presence of different counteranions could potentially modulate the formation of organometallic complexes due to their improved solubility and the stabilizing effect of anion participation.

Table 4. Results of the halide exchange in pyridinium, benzimidazolium and imidazolium salts **[bmpy][I]**, **1·Cl** and **2·I**.

Anion	Solvent	[bmpy][I]		1·Cl		2·I	
		Yield (%) [a]	I^- (ppm) [b]	Yield (%) [a]	Cl^- (ppm) [b]	Yield (%) [a]	I^- (ppm) [b]
AcO^-	CH_3OH	84	<20	95	<6	100	<20
AcO^-	CH_3CN	100	<20	—		—	
BzO^-	CH_3OH	100	<20	92	<6	95	<20
BzO^-	CH_3CN	—		100	<6	—	
(*S*)-Lactate$^-$	CH_3OH	100	<20	98	<6	100	<20
$MeSO_3^-$	CH_3OH	100	<20	91	<6	90	<20
$MeSO_3^-$	CH_3CN	—		100	<6	100	
$Bu_2PO_4^-$	CH_3OH	100	<20	95	<6	97	<20
PF_6^-	CH_3OH	100	<20	100	<6	100	<20
BF_4^-	CH_3OH	98	<40	79	<6	100	<20
BF_4^-	CH_3CN	—		100	<6	—	
$CF_3SO_3^-$	CH_3OH	100	<20	88	<6	95	<20
$CF_3SO_3^-$	CH_3CN	—		95	<6	—	
SCN^-	CH_3OH	100	ND	91	ND	100	ND
SCN^-	CH_3CN	—		97	ND	—	
Ph_4B^-	CH_3CN	—		82	<6	—	

ND: Not Determined. [a] Yield of the recovered new ion pair. Yields ≥95% in CH_3OH were not further examined in CH_3CN; [b] Halide contents after anion exchange determined by silver chromate test.

Two examples of quaternary ammonium salts were selected from the API family to confirm the efficiency of the method with this type of ILs. The choline lactate (**[Cho][Lact]**) [44] was quantitatively prepared from the corresponding **[Cho]I** using the AER (Lact$^-$ form) in methanol. Didecyldimethylammonium bromide (**[d_2m_2N]Br**) was transformed to the antibacterial-anti-inflammatory didecyldimethylammonium ibuprofenate **[d_2m_2N][Ibu]** [45].

This hydrophobic ammonium salt required the lipophylic solvent mixture CH_3CN:CH_2Cl_2 (3:7) to afford the quantitatively iodide-to-ibuprofenate switch, since in acetonitrile the yield was only 61% (Scheme 7 and Table 5).

Scheme 7. AER (A^- form) method. Quaternary ammonium salts.

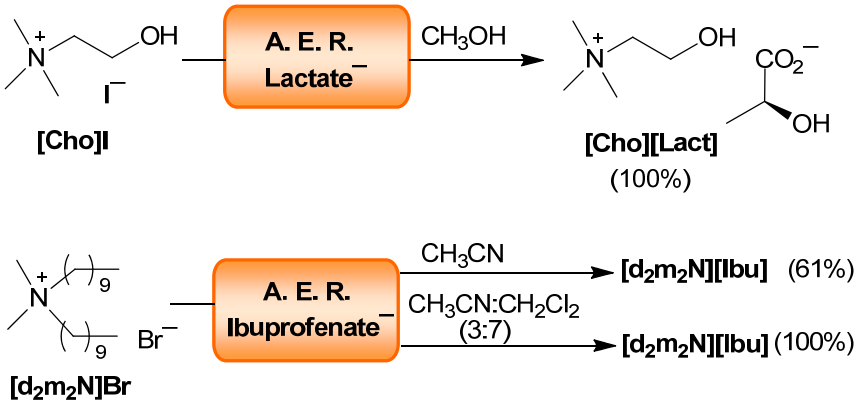


Table 5. The halide exchange in quaternary ammonium salts **[Cho]I** and **[d_2m_2N]Br**.

Cation	Anion	Solvent	Yield (%) [a]	I^- (ppm) [b]
Cho	(*S*)-Lactate$^-$	CH_3OH	100	<20
d_2m_2N	Ibu$^-$	CH_3CN	61	<13
	Ibu$^-$	CH_3CN: CH_2Cl_2 (3:7)	100	<13

[a] Yield of the recovered new ion pair; [b] Halide contents after anion exchange determined by silver chromate test.

The quaternary heteroaromatic and ammonium ILs prepared taking advantage of the AER (A^- form) method in organic solvents were characterized by ^{1}H-NMR, electrospray ionization mass spectrometry in the negative mode and the halide content was determined by the silver chromate test. When the recovery of the new ion pair **[IL][A]** was ≤95%, a new assay was performed using a less polar organic solvent, which improved the yield in the range of 95% to 100%. As mentioned above, the use of an anion exchange resin implies the possibility of sorbet contamination [13,46], so, nano-particulates may be an issue to analyze. The analysis of possible nano-particulate contamination was, however, beyond the scope of the present study.

Recapping the results, the AER (A^- form) method applied to different examples of quaternary heteroaromatic salts and ionic liquids permitted the halide to be swapped for assorted anions in excellent yields of ≥95% when the appropriate organic solvent or solvent mixture was used. It was confirmed that the AER (A^- form) method is efficient with imidazolium-based ILs, improving the currently operative procedures of classical counteranion exchange. Against a large pool of quaternary heteroaromatic and ammonium salts, we limited ourselves to the eleven examples shown in Figure 1 to validate the AER (A^- form) method in non-aqueous media.

3. Experimental

3.1. General

Ion exchanger resin Amberlyst A-26 (Aldrich, OH^- form), **[hmim]Cl**, **[dmim]Cl**, **[Cho]I** and **[d_2m_2N]Br** together with all acids, ammonium salts, reagents and solvents were purchased from commercial suppliers, unless mentioned otherwise, and used without further purification. All solvents were reagent grade and methanol and THF were distilled prior to use. **[bmim]I** [32], **[bmim]Br** [32], **[bbim]I** [32], **[bbim]Br** [32], **[mmim]I** [32], **[bm_2im]Br** [47], **[bmpy]I** [48], and **1·Cl** [49] were prepared according with the literature. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) spectrometer at 298 K. ^{1}H and ^{13}C chemical shifts were referenced with TMS as an internal reference. Mass spectrometric analyses were performed on a LC/MSD-TOF (2006) mass spectrometer with a pumping system HPLC Agilent 1100 from Agilent Technologies at Serveis Científico-Tècnics of universitat de Barcelona. The pH was measured with benchmeter pH1100 (Eutech Instrunments, Nijkerk, The Netherlands), using Hamilton Flushtrode pH electrode for hydroalcoholic solutions.

3.2. Loading the AER (OH^- Form) with Acids or Ammonium Salts

A glass column (1 cm diameter) packed with 2.5 g (~3 cm^3) of commercial wet strongly basic anion exchange Amberlyst A-26 (OH^- form) was washed with water, and the column bed was equilibrated progressively with water-solvent mixtures until reaching the selected solvent media used afterwards for anion loading (~25 mL of each solvent mixture). A 1% acid or ammonium salt solution in the appropriate solvent was passed slowly through the resin until the eluates had the same pH value as the original selected acid solution, and then the resin was washed generously with solvent until constant pH. The process was carried out at room temperature, using gravity as the driving force.

3.3. Anion Exchange: General Procedure

A solution of the imidazolium salt (0.5–0.6 mmol) in 10 mL of the selected solvent was passed slowly through a column packed with ~3 cm^3 of Amberlyst A-26 (A^- form), and then washed with 25 mL of solvent. The combined eluates were evaporated, and the residue obtained was dried in a vacuum oven at 60 °C with P_2O_5 and KOH pellets.

3.4. Silver Chromate Test

The amount of halide contents was determined by a silver chromate test following a similar protocol to that described by Sheldon and co-workers [31]. An aqueous solution (5 mL) of potassium chromate (5% p/v in Milli-Q water, 0.257 M) was added to the sample (5–10 mg). To 1 mL of the resulting dark yellow solution was added a minimum amount of silver nitrate aqueous solution (0.24% p/v in Milli-Q water, 0.014 M). A persistent red suspension of silver chromate would be observed if the sample was free of halide. The minimum measurable amount of silver nitrate aqueous solution was 0.011 mL; consequently, the detection limit is approx. 6 ppm for Cl^-, 13 ppm for Br^- or 20 ppm for I^-. The halide content was determined at least twice for each sample.

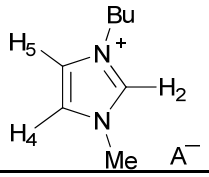
3.5. 1,3-Dibutyl-5,6-dimethylbenzimidazolium Iodide (**2·I**)

A suspension of 5,6-dimethyl-1*H*-benzimidazole (1.00 g, 6.84 mmol) and NaH (0.40 g, 16.66 mmol) in dry THF (100 mL) was stirred under argon atmosphere at 60 °C for 1 h, and then 1-iodobutane (1.50 g, 8.15 mmol) was added. The reaction mixture was stirred at 65 °C for 48 h, and then 5 mL of ethanol were added. The solvent was evaporated to dryness, and the residue was treated with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic solution was dried over anhydrous Na_2SO_4, filtered and the solvent was eliminated under vacuum. A mixture of the previous yellow oil (1.34 g, 6.62 mmol) and 1-iodobutane (1.23 g, 6.70 mmol) was stirred under argon atmosphere at 85 °C for 20 h. The reaction mixture was washed with dry diethyl ether (3 × 25 mL) in an ultrasonic bath, providing the pure **2·I** as a white solid (2.47 g, 93% yield). M.p. 150–1 °C. δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.99 (6H, t, J = 7.4 Hz, N-C_3H_6-CH_3), 1.45 (4H, m, N-C_2H_4-CH_2-CH_3), 2.02 (4H, m, N-CH_2-CH_2-C_2H_5), 2.47 (6H, s, C(5,6)-Me), 4.56 (4H, t, J = 7.4 Hz, N-CH_2-C_3H_7), 7.42 (2H, s, C(4,7)-H) and 11.01 (1H, s, C(2)-H). δ_C (75.4 MHz, $CDCl_3$) 13.5, 19.8, 20.7, 31.3, 47.3, 112.8, 129.8, 137.5, 140.4. HRMS-ESI(+) Calcd for $C_{17}H_{27}N_2$ $[M]^+$ 259.2169, found 259.2167.

Melting points of compounds **2·A**: **2·MeSO$_3$**, 62–3 °C; **2**·Bu$_2$PO$_4$, 56–7 °C; **2·PF$_6$**, 85–6 °C; **2·BF$_4$**, 109–110 °C; **2·CF$_3$SO$_3$**, 78–9 °C; **2·SCN**, 64–5 °C; **2·AcO**, **2·BzO** and **2·Lact** are oily compounds at room temperature

*3.6. ^{1}H-NMR Data of Compounds **[bmim][A]** (Table 6), **[bbim][A]** (Table 7), **[mmim][A]** (Table 8), **[hmim][A]** (Table 9), **[dmim][A]** (Table 9), **[bm$_2$im][A]** (Table 10), **[bmpy][A]** (Table 11), **1·A** (Table 12), **2·A** (Table 13), **[Cho][A]** (Table 14) and **[d$_2$m$_2$N][A]** (Table 14)*

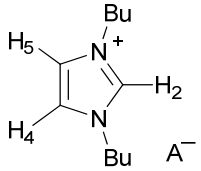
Table 6. ^{1}H-NMR chemical shift values of 1-butyl-3-methylimidazolium salt **[bmim][A]** (300 MHz) at 298 K [a].



Anion	Solvent	H-2	H-4	H-5	Bu	Me	A$^-$
AcO$^-$	$CDCl_3$	11.35	7.09	7.08	4.30; 1.86; 1.37; 0.96	4.06	1.99
BzO$^-$	$CDCl_3$	11.00	7.09	7.09	4.29; 1.84; 1.33; 0.92	4.08	8.10; 7.33
(*S*)-Lactate$^-$	$CDCl_3$	11.19	7.17	7.17	4.31; 1.89; 1.38; 0.98	4.08	3.46; 1.41
$MeSO_3^-$	$CDCl_3$	10.21	7.25	7.20	4.28; 1.87; 1.38; 0.97	4.05	2.80
$Bu_2PO_4^-$	$CDCl_3$	10.19	7.36	7.23	4.25; 1.80; 1.33; 0.88	4.00	3.80;1.54;1.33; 0.88
I$^-$ [b]	$CDCl_3$	10.27	7.52	7.44	4.35; 1.93; 1.41; 0.99	4.14	
Br$^-$	$CDCl_3$	10.41	7.46	7.37	4.35; 1.91; 1.40; 0.98	4.13	
F$^-$	$CDCl_3$	(c)	7.50	7.33	4.29; 1.87; 1.36; 0.95	4.06	
Cl$^-$	$CDCl_3$	10.99	7.31	7.24	4.33; 1.91; 1.40; 0.98	4.13	
PF_6^-	$CDCl_3$	9.07	7.26	7.23	4.20; 1.88; 1.38; 0.97	3.98	
NO_3^-	$CDCl_3$	10.02	7.35	7.30	4.25; 1.88; 1.38; 0.97	4.02	
ClO_4^-	$CDCl_3$	9.15	7.30	7.26	4.23; 1.89; 1.39; 0.98	4.02	
BF_4^-	$CDCl_3$	8.98	7.28	7.24	4.21; 1.87; 1.39; 0.97	3.98	
$CF_3SO_3^-$	$CDCl_3$	9.27	7.32	7.28	4.21; 1.88; 1.38; 0.97	3.99	
SCN$^-$	$CDCl_3$	9.59	7.36	7.31	4.32; 1.92; 1.41; 0.99	4.11	
Ibu$^-$	$CDCl_3$	9.86	7.10	7.02	4.02; 1.66; 1.24; 0.87	3.71	7.26; 6.95; 3.53; 2.35; 1.75; 1.39; 0.82
AcO$^-$	CD_3CN	9.25	7.35	7.32	4.14; 1.80; 1.31; 0.93	3.84	1.66
BzO$^-$	CD_3CN	9.43	7.29	7.28	4.19; 1.80; 1.30; 0.92	3.86	7.93; 7.27
$MeSO_3^-$	CD_3CN	8.63	7.37	7.34	4.16; 1.80; 1.31; 0.94	3.83	2.43
I$^-$	CD_3CN	8.56	7.39	7.35	4.14; 1.81; 1.31; 0.94	3.83	
Cl$^-$	CD_3CN	9.04	7.39	7.36	4.15; 1.80; 1.31; 0.93	3.84	
PF_6^-	CD_3CN	8.42	7.35	7.31	4.11; 1.79; 1.30; 0.93	3.80	
NO_3^-	CD_3CN	8.58	7.37	7.34	4.13; 1.81; 1.31; 0.94	3.82	
ClO_4^-	CD_3CN	8.43	7.37	7.35	4.12; 1.81; 1.32; 0.94	3.82	
BF_4^-	CD_3CN	8.43	7.36	7.33	4.12; 1.82; 1.32; 0.94	3.81	
$CF_3SO_3^-$	CD_3CN	8.43	7.36	7.33	4.12; 1.80; 1.32; 0.94	3.81	
SCN$^-$	CD_3CN	8.49	7.37	7.34	4.13; 1.80; 1.30; 0.94	3.82	
Ph_4B^-	$CDCl_3$	4.54	6.01	5.84	3.16; 1.33; 1.13; 0.89	2.76	7.52; 6.97; 6.78
Ph_4B^-	CD_3CN	8.19	7.27 [d]	7.27 [d]	4.05; 1.77; 1.30; 0.93	3.74	7.27; 6.99; 6.84
Ph_4B^-	DMSO-d_6	9.06	7.74	7.67	4.13; 1.75; 1.24; 0.89	3.82	7.16; 6.91; 6.78

[a] Solution concentrations are 0.02 M; [b] Unambiguous assignments were made by NOESY-1D (400 MHz); [c] Signal not observed; [d] Included in the phenyl signal.

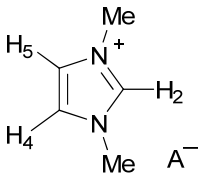
Table 7. ^{1}H-NMR chemical shift values of 1,3-dibutylimidazolium salt **[bbim][A]** (300 MHz) at 298 K [a].



Anion	Solvent	H-2	H-4,5	Bu	A$^-$
AcO^-	$CDCl_3$	11.32	7.14	4.35; 1.86; 1.39; 0.97	2.01
BzO^-	$CDCl_3$	11.40	7.16	4.34; 1.87; 1.35; 0.93	8.10; 7.32
(*S*)-Lactate$^-$	$CDCl_3$	11.29	7.14	4.33; 1.87; 1.37; 0.96	4.02; 1.39
$MeSO_3^-$	$CDCl_3$	9.73	7.51	4.30; 1.88; 1.37; 0.96	2.75
$Bu_2PO_4^-$	$CDCl_3$	11.05	7.11	4.37; 1.88; 1.40; 0.94	3.87; 1.62; 1.40; 0.94
I^-	$CDCl_3$	10.34	7.38	4.38; 1.95; 1.42; 0.99	
Br^-	$CDCl_3$	10.58	7.42	4.36; 1.90; 1.37; 0.95	
F^-	$CDCl_3$	(b)	7.17	4.30; 1.89; 1.40; 0.98	
Cl^-	$CDCl_3$	11.05	7.23	4.38; 1.92; 1.41; 0.98	
PF_6^-	$CDCl_3$	9.05	7.23	4.24; 1.88; 1.39; 0.98	
NO_3^-	$CDCl_3$	9.89	7.39	4.25; 1.86; 1.33; 0.94	
ClO_4^-	$CDCl_3$	9.24	7.38	4.26; 1.88; 1.37. 0.96	
BF_4^-	$CDCl_3$	9.12	7.36	4.23; 1.87; 1.36; 0.95	
$H_2PO_4^-$	$CDCl_3$	10.59	7.31	4.40; 1.84; 1.34; 0.92	
HSO_4^-	CD_3CN	10.84	7.40	4.39; 1.84; 1.34; 0.91	
$CF_3SO_3^-$	$CDCl_3$	9.49	7.28	4.26; 1.88; 1.38; 0.98	
SCN^-	$CDCl_3$	9.18	7.34	4.25; 1.88; 1.38; 0.97	
Ph_4B^-	$CDCl_3$	(b)	5.81	3.10; 1.30; 1.13; 0.89	7.50; 6.98; 6.82
Ph_4B^-	DMSO-d_6	9.19	7.79	4.15; 1.77; 1.26; 0.90	7.18; 6.92; 6.78

[a] Solution concentrations are 0.02 M. [b] Signal not observed.

Table 8. ^{1}H-NMR chemical shift values of 1,3-dimethylimidazolium salt **[mmim][A]** (300 MHz) at 298 K [a].



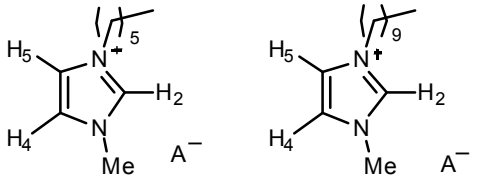
Anion	Solvent	H-2	H-4,5	Me	A$^-$
AcO^-	CD_3CN	9.05	7.32	3.83	1.69
BzO^-	CD_3CN	9.29	7.33	3.85	7.93; 7.28
(*S*)-Lactate$^-$	$CDCl_3$	11.04	7.15	4.03	3.80; 1.38
$MeSO_3^-$	CD_3CN	8.58	7.33	3.83	2.43
$Bu_2PO_4^-$	$CDCl_3$	10.88	7.15	4.04	3.86; 1.61; 1.39; 0.90
I^-	CD_3CN	8.48	7.34	3.83	
Cl^-	CD_3CN	8.57	7.34	3.83	
PF_6^-	CD_3CN	8.38	7.32	3.82	
NO_3^-	CD_3CN	8.57	7.34	3.83	
ClO_4^-	CD_3CN	8.45	7.33	3.82	

Table 8. *Cont.*

Anion	Solvent	H-2	H-4,5	Me	A^-
BF_4^-	CD_3CN	8.43	7.33	3.82	
$H_2PO_4^-$	$CDCl_3$	10.26	7.30	4.09	
HSO_4^-	$CDCl_3$	10.19	7.34	4.09	
$CF_3SO_3^-$	CD_3CN	8.45	7.33	3.82	
SCN^-	CD_3CN	8.44	7.33	3.83	

[a] Solution concentrations are 0.02 M.

Table 9. ^{1}H-NMR chemical shift values of imidazolium salts **[hmim][A]** and **[dmim][A]** in $CDCl_3$ (300 MHz) at 298 K [a,b].

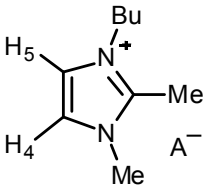


[hmim][A] **[dmim][A]**

Cation	Anion	H-2	H-4	H-5	C_nH_{n+1}	Me	A^-
hmim	Cl^-	10.80	7.44	7.31	4.30; 1.89; 1.30; 0.86	4.11	–
	Ibu^-	9.72	7.08	7.01	4.05; 1.74; 1.26; 0.86	3.75	7.28; 7.01; 3.54; 2.37; 1.78; 1.41; 0.86
dmim	Cl^-	10.82	7.38	7.27	4.32; 1.89; 1.27; 0.86	4.12	–
	Ibu^-	10.58	7.01	6.99	4.11; 1.78; 1.25; 0.87	3.81	7.31; 6.98; 3.60; 2.39; 1.79; 1.46; 0.87

[a] Solution concentrations are in the range of 0.015 to 0.025 M; [b] H-4 and H-5 assignments were made according **[bmim]I**.

Table 10. ^{1}H-NMR chemical shift values of 1-butyl-2,3-dimethylimidazolium salt **[bm$_2$im][A]** in $CDCl_3$ (300 MHz) at 298 K [a].



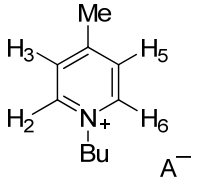
Anion	H-4	H-5	Me-2	Me-3	Bu	A^-
AcO^-	7.58	7.36	2.59	3.82	4.06; 1.67; 1.26; 0.86	1.72
BzO^-	7.54	7.27	2.50	3.71	3.90; 1.58; 1.23; 0.85	7.97; 7.27
(S)-Lactate$^-$	7.49	7.26	2.70	3.92	4.12; 1.79; 1.40; 0.98	3.87; 1.30
$MeSO_3^-$	7.47	7.27	2.69	3.94	4.14; 1.80; 1.38; 0.98	2.74
$Bu_2PO_4^-$	7.55	7.27	2.68	3.92	4.13; 1.76; 1.37; 0.96	3.77; 1.56; 1.37; 0.89
Br^{-b}	7.76	7.56	2.83	4.04	4.24; 1.81; 1.40; 0.98	
I^-	7.60	7.46	2.80	3.98	4.18; 1.80; 1.39; 0.94	
PF_6^-	7.46	7.30	2.70	3.90	4.11; 1.79; 1.40; 0.96	
BF_4^-	7.40	7.27	2.68	3.88	4.10; 1.79; 1.40; 0.97	
$CF_3SO_3^-$	7.32	7.22	2.66	3.86	4.09; 1.80; 1.40; 0.97	
NCS^-	7.43	7.32	2.77	3.96	4.17; 1.83; 1.43; 0.98	

Table 10. *Cont.*

Anion	H-4	H-5	Me-2	Me-3	Bu	A^-
Ph_4B^-	6.38	6.28	2.39	2.98	3.36; 1.52; 1.25; 0.92	7.46; 6.99; 6.83
Ph_4B^{-c}	7.63	7.60	2.56	3.73	4.09; 1.68; 1.29; 0.90	7.17; 6.92; 6.78
Ibu^-	7.30	7.07	2.37	3.57	3.88; 1.56; 1.22; 0.85	7.23; 6.94; 3.45; 2.33; 1.73; 1.33; 0.81

[a] Solution concentrations are 0.02 M; [b] Unambiguous assignments were made by NOESY-1D (400 MHz); [c] In DMSO-d_6.

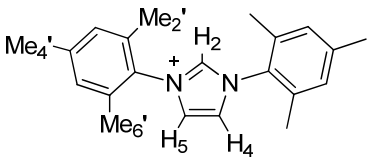
Table 11. ^{1}H-NMR chemical shift values of 1-butyl-4-methylpyridinium salt **[bmpy][A]** in $CDCl_3$ (300 MHz) at 298 K [a].



Anion	H-2,6	H-3,5	Me	Bu	A^-
AcO^-	9.35	7.82	2.62	4.82; 1.96; 1.35; 0.94	1.96
BzO^-	8.94	7.70	2.47	4.67; 1.82; 1.25; 0.83	8.00; 7.31
(S)-$Lactate^-$	9.05	7.81	2.57	4.65; 1.88; 1.35; 0.87	3.89; 1.26
$MeSO_3^-$	9.09	7.83	2.57	4.65; 1.91; 1.32; 0.87	2.68
$Bu_2PO_4^-$	9.36	7.83	2.53	4.72; 1.89; 1.30; 0.83	3.78; 1.50; 1.30; 0.83
I^-	9.24	7.90	2.66	4.84; 2.00; 1.41; 0.95	
PF_6^-	8.60	7.80	2.66	4.54; 1.95; 1.39; 0.95	
BF_4^-	8.73	7.82	2.66	4.60; 1.95; 1.39; 0.95	
$CF_3SO_3^-$	8.80	7.82	2.65	4.60; 1.94; 1.38; 0.94	
NCS^-	8.94	7.91	2.70	4.77; 2.03; 1.44; 0.99	

[a] Solution concentrations are 0.02 M.

Table 12. ^{1}H-NMR chemical shift values of 1,3-bis(mesityl)imidazolium salt **1·A** in $CDCl_3$ (300 MHz) at 298 K [a].



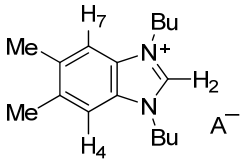
Anion	H-2	H-4,5	Me-2',6'	Me-4'	H-3'	A^-
AcO^-	11.54	7.46	2.20	2.35	7.04	2.16
BzO^-	11.03	7.44	2.07	2.25	6.87	7.63; 7.14
(S)-$lactate^-$	10.31	7.56	2.10	2.32	7.00	3.65; 1.04
$MeSO_3^-$	9.83	7.63	2.09	2.31	6.98	2.31
$Bu_2PO_4^-$	10.76	7.67	2.12	2.30	6.97	3.43; 1.32; 1.20; 0.79
Cl^-	10.98	7.57	2.20	2.34	7.03	
PF_6^-	8.77	7.57	2.14	2.37	7.07	
BF_4^-	9.19	7.57	2.09	2.32	6.99	
$CF_3SO_3^-$	9.29	7.57	2.09	2.34	7.01	

Table 12. *Cont.*

Anion	H-2	H-4,5	Me-2',6'	Me-4'	H-3'	A^-
SCN^-	9.70	7.63	2.19	2.37	7.08	
Ph_4B^-	6.32	7.06	2.02	2.20	6.77	7.30; 6.88; 6.77
Ph_4B^{-b}	9.64	8.25	2.11	2.35	7.20	7.18; 6.92; 6.78

[a] Solution concentrations are in the range of 0.01 to 0.02 M; [b] In DMSO-d_6.

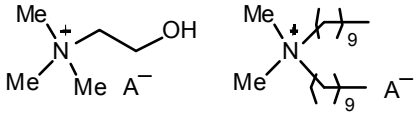
Table 13. ^{1}H-NMR chemical shift values of 1,3-dibutyl-5,6-dimethylbenzimidazolium salt **2·A** in $CDCl_3$ (300 MHz) at 298 K [a].



Anion	H-2	H-4,7	Me	Bu	A^-
AcO^-	11.86	7.37	2.46	4.55; 1.96; 1.42; 0.97	2.03
BzO^-	11.91	7.37	2.45	4.56; 2.00; 1.41; 0.93	8.11; 7.34
(S)-lactate$^-$	11.39	7.36	2.43	4.49; 1.92; 1.37; 0.93	4.03; 1.37
$MeSO_3^-$	10.63	7.40	2.47	4.53; 1.98; 1.44; 0.99	2.84
$Bu_2PO_4^-$	11.52	7.36	2.45	4.57; 1.96; 1.41; 0.97	3.90; 1.62; 1.41; 0.90
I^-	10.98	7.43	2.46	4.55; 2.02; 1.46; 0.99	
PF_6^-	9.25	7.43	2.48	4.41; 1.97; 1.43; 0.99	
BF_4^-	9.33	7.48	2.45	4.43; 1.94; 1.40; 0.94	
$CF_3SO_3^-$	9.86	7.42	2.47	4.48; 1.97; 1.43; 0.98	
SCN^-	10.13	7.43	2.48	4.53; 2.02; 1.47; 1.00	

[a] Solution concentrations are 0.02 M.

Table 14. ^{1}H-NMR chemical shift values of quaternary ammonium salts **[Cho][A]** and [**d_2m_2N][A]** (300 MHz) at 298 K.



[Cho][A] **[d_2m_2N][A]**

Cation	Anion	Solvent	Me	N^+-CH_2-CH_2-OH	A^-
Cho	I^-	CD_3CN	3.12	3.95; 3.41; 3.59(OH)	–
	(*S*)-Lactate$^-$	CD_3CN	3.13	3.95; 3.43; 3.67(OH)	3.78; 1.19
				N^+-C_nH_{n+1}	
d_2m_2N	Br^-	$CDCl_3$	3.41	3.51; 1.65; 1.30; 0.88	–
	Ibu^-	$CDCl_3$	3.01	3.10; 1.52; 1.26; 0.88	7.30; 7.00; 3.57; 2.39; 1.81; 1.42; 0.88

4. Conclusions

Faced with a large variety of quaternary imidazolium and ammonium salts, the present study using an anion exchange resin (A^- form) in non-aqueous media was based on a choice of eleven examples

taken from the IL pool **[IL]X** that could serve to evaluate the halide-for-anion swap. Significant aspects of the reported AER (A^- form) process are: (i) the anion loading of the AER (OH^- form) with acids and ammonium salts in solvent mixtures of different polarities according to the hydrophobicity of the anion source; (ii) the anion exchange using the AER (A^- form) method in organic solvents was easily applied to several imidazolium, benzimidazolium, pyridinium and ammonium salts, the halide-for-anion exchange progressing in excellent to quantitative yields. Depending on the hydrophobic nature of the targeted organic salts, the counteranion exchange was accomplished in organic solvents of variable polarity and dipolar nonhydroxylic organic solvent mixtures ranging from the lowest proportions of water or methanol to lipophylic solvent mixtures such as CH_3CN:CH_2Cl_2 (3:7).

On the whole, the AER (A^- form) method in organic solvents is a method of choice for exchanging the halide anions for a variety of anions in quaternary heteroaromatic and ammonium salts, simultaneously removing halide impurities, which is often a troublesome task. This anion exchange method could be adapted to a wide array of charged molecules crucial to advances in interdisciplinary fields in chemistry.

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Sample Availability: Samples of all compounds are available from the authors.

- **A halide-for-anion swap using an anion exchange resin (A^- form) method: revisiting imidazolium-based anion receptors and sensors.**

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A Halide-for-Anion Swap Using an Anion-Exchange Resin (A^- Form) Method: Revisiting Imidazolium-Based Anion Receptors and Sensors[‡]

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Keywords: Supramolecular chemistry / Anions / Anion recognition / Sensors / Receptors / Ion exchange

Faced with an extensive pool of imidazolium-based systems, the present study was based on selected examples of bis(imidazolium) models for anion recognition to broaden the applicability of counteranion exchange by using the anion-exchange resin (AER) (A^- form) method in nonaqueous media. Relying on the hydrophobicity of the quaternary imidazolium salt for counteranion exchange, the AER (A^- form) method was performed in organic solvents of different polarity, such as CH_3OH and CH_3CN. Anion exchange proceeded in excellent to quantitative yields, simultaneously removing halide impurities—often a troublesome purification task. The results of electrospray mass spectrometry [ESI(+)-MS] analysis focused on the gas-phase behavior of the dicationic cyclophane prototype **5**·2Cl and the open-chain compound pairs **4**·2Br and **15**·2Br are briefly described.

Introduction

The distinct facets of anions allow them to play a variety of roles in supramolecular chemistry, as reflected by current advances in anion recognition.[2,3] A survey of molecular and supramolecular charged systems has shown that different counteranion effects in solution can modulate their functions and representative developments in tailored mechanostereochemical systems have been authoritatively discussed.[4] It should be recalled that efficient template macrocyclization reactions in the 1990s normally involved the use of cations and neutral molecules as templates, while approaches with anion templates were far less common. The following decade saw progress towards anion-templated synthesis in supramolecular and coordination chemistry, the use of strategic anion templates, and anion-templated assembly. At the same time, imidazolium-based systems became increasingly useful in a widening range of fields that included anion-recognition chemistry and ionic liquids (ILs), as well as N-heterocyclic carbenes (NHCs).[5]

The imidazolium pool is continuing to progress, in particular, ILs have featured extensively in recent literature.[5–14] The synthesis, counteranion exchange, and purity of imidazolium ILs have been the subject of numerous studies together with other chemical and physicochemical properties, such as counteranion effects, for example, basicities, shapes, and coordination abilities,[9–11] and the acidity of imidazolium cations.[5,12] A widespread synthetic route to imidazolium systems is a subclass of the Menschutkin reaction, giving the targeted charged system in which the counteranion(s), the halide ion(s), can be exchanged by different methods. Notwithstanding the apparent directness of the counteranion-exchange process, the isolation and purification of pure imidazolium quaternary salts can be troublesome when different species present in the solution have similar solubility. After habitual halide-ion exchange with another inorganic salt (MA), the halide-containing, by-product salts can be removed by extraction or precipitation followed by filtration.[5] This procedure has been applied extensively with positively charged compounds, such as ILs,[1,7c,8,9] and systems with heteroaromatic quaternary moieties, especially pyridinium and imidazolium rings, and, to a lesser extent, azinium or azolium nuclei.

Despite the utility of imidazolium ILs and current advances in imidazolium anion receptors and sensors, counteranion exchange with anion-exchange resins (AERs) has been rather neglected and only a few examples of imidazolium-based ILs take advantage of useful AERs (OH^- and A^- forms).[1,5,9] Exploiting our preliminary results on the counteranion exchange of imidazolium ILs using the AER (A^- form) method in hydroalcoholic solutions, we have reported studies expanding the scope of the halide-for-anion swap in nonaqueous media for representative hydrophobic imidazolium ILs. Conditioned by the hydrophobicity of the ion pairs, different non-hydroxylic organic solvents were used to swap the halide ion for assorted anions in both lipophilic imidazolium species and low hydrophilicity anions, giving excellent to quantitative yields.[1]

With the aim to broadening the usefulness of halide-to-anion exchange by using an AER (A^- form) method in organic solvents, the present study examines the value of this method for imidazolium anion receptors and sensor mod-

[‡] Imidazolium-Based Frameworks, 23. Part 22: Ref.[1]

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els: the (anthrylmethyl)imidazolium chloride (**1**·Cl) fluorescent probe,[13] the dicationic protophane counterpart **2**·2Cl,[14] the open-chain compound **3**·2Cl,[15] and a reagent for anion detection by ESI-MS **4**·2Br,[16] as well as the dicationic [1$_4$]imidazoliophane anion-receptor prototype **5**·2Cl,[17,18] and calix[4]arenes **6**·2Br[19,20] and **7**·2Br (Figure 1 and Table S1 in the Supporting Information).

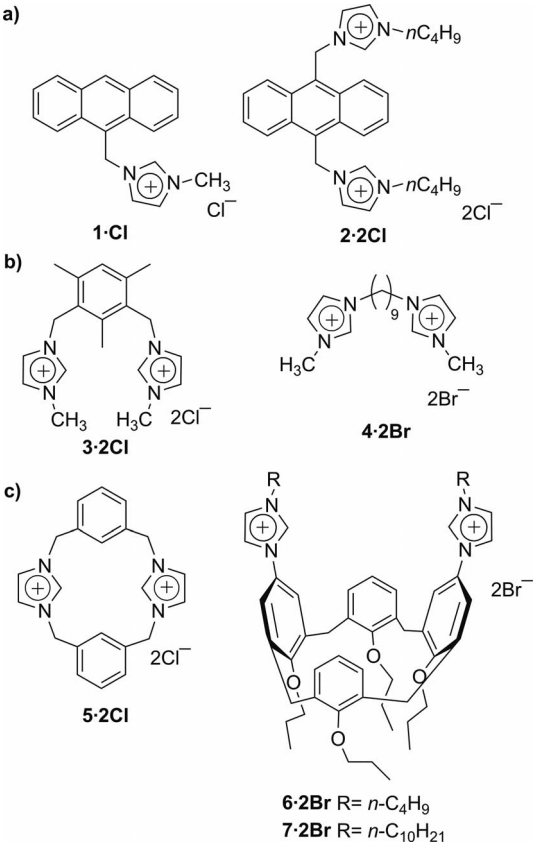
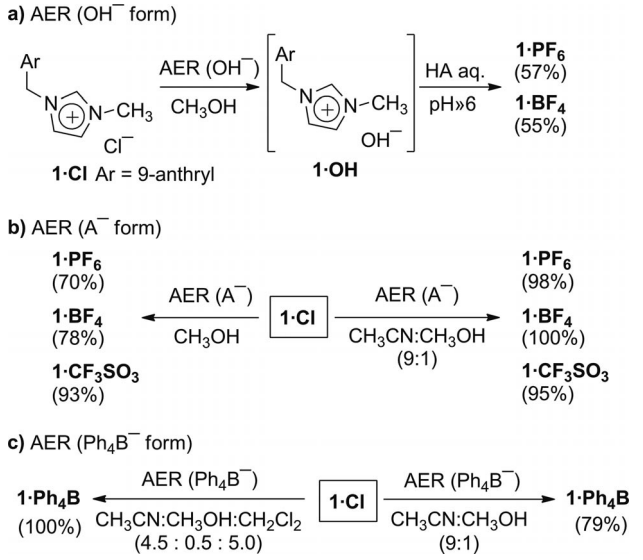


Figure 1. Imidazolium-based systems. (a) Illustrative fluorogenic anion sensors: (anthrylmethyl)imidazolium chloride **1**·Cl and dicationic protophane **2**·Cl. (b) Open-chain bis(imidazolium) systems **3**·Cl and **4**·2Br. (c) Bis(imidazolium)cyclophane anion-receptor prototype **5**·2Cl and calix[4]arenes **6**·2Br and **7**·2Br.

Results and Discussion

An illustrative example of a less polar imidazolium salt for testing anion exchange could be **1**·Cl and the salts **1**·A (A = anion) recently reported by Dyson and co-workers.[13] They described the transformation of **1**·Cl into salts **1**·A (A = PF_6, BF_4, and CF_3SO_3), following classical counteranion exchange with inorganic salts (MA) in yields from 70 to 89% (see Tables S1 and S2 in the Supporting Information).[13] We first examined the transformation of **1**·2Cl into **1**·PF_6 and **1**·BF_4 with both AER (OH^- form) and AER (A^- form) methods. A solution of **1**·2Cl in methanol was passed through a column packed with an AER (OH^- form) and solutions of H_2O/HPF_6 or H_2O/BF_4 were then added to the eluates to give pH = 6. The precipitate of **1**·PF_6 or **1**·BF_4 was filtered and dried, resulting in only moderate yields (ca. 56%). By using the AER (A^- form) method in methanol the yields increased to about 74%; the best results were observed when a solution of **1**·2Cl in CH_3CN/CH_3OH (9:1) was passed through a column packed with the corresponding AER (A^- form). The eluates were then evaporated to give the pure ion pairs **1**·PF_6 or **1**·BF_4 in nearly quantitative yield (Scheme 1 and Table S2 in the Supporting Information).



Scheme 1. Transformation of **1**·Cl into **1**·PF_6, **1**·BF_4, **1**·CF_3SO_3, and **1**·Ph_4B: (a) AER (OH^- form) method; (b) AER (A^- form) method in organic solvents; (c) AER (Ph_4B^- form) in organic solvent mixtures.

The anion swap of Cl^- for PF_6^-, BF_4^-, $CF_3SO_3^-$, and Ph_4B^- merits a brief comment. When an AER (A^- form) was conveniently loaded with PF_6^-, BF_4^-, or $CF_3SO_3^-$, the anion exchange of **1**·Cl in methanol proceeded in variable yields of ≥70%. Due to the decreasing solubility of the ion pairs **1**·PF_6, **1**·BF_4, and **1**·CF_3SO_3 in methanol, the AER (A^- form) method in acetonitrile was then assayed, but the starting imidazolium salt, **1**·2Cl, was insoluble in this solvent. However, the solvent mixture CH_3CN/CH_3OH (9:1) permitted counteranion exchange of **1**·2Cl to afford **1**·PF_6, **1**·BF_4, and **1**·CF_3SO_3 in nearly quantitative yields. For the new targeted imidazolium salt, **1**·Ph_4B, the hydrophobic nature of the tetraphenylborate anion was evident because when a solution of **1**·Cl in CH_3CN/CH_3OH (9:1) was passed through an AER (Ph_4B^- form) a precipitate was formed inside the column and the hydrophobic ion pair **1**·Ph_4B was obtained in just 79% yield after additional solvent was passed through the resin. A more lipophilic solvent mixture, $CH_3CN/CH_3OH/CH_2Cl_2$ (4.5:0.5:5), produced the chloride-to-tetraphenylborate exchange quantitatively (see Scheme 1, Table S2 in the Supporting Information).

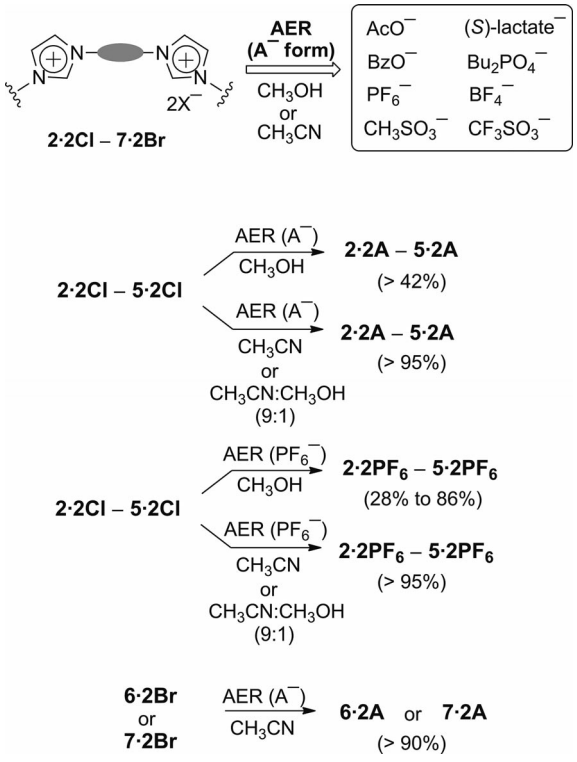
Bis(imidazolium) Systems

Faced with a large pool of imidazolium-based systems,[5,6] we limited ourselves to six examples, **2**·2Cl–**7**·2Br,

to analyze the AER (A^- form) method in organic solvents (Figure 1 and Table S1 in the Supporting Information). Imidazolium systems with signaling unit(s) are currently being developed as anion sensors, such as the fluorescent dicationic protophane **2**·2Cl for the recognition of pyrophosphate.[14] Bis(imidazolium) protophane **3**·2Cl has been used as a direct precursor of metal complexes in the domain of N-heterocyclic carbenes (NHCs)[15] and the open-chain dication **4**·2Br has been found to be suitable for use as a reagent for anion detection by ESI(+)-MS.[16] Dicationic cyclophane **5**·2Cl has arisen as a prototype for intermolecular interactions driven by nonclassical $(C–H)^+\cdots Cl$ hydrogen bonds. Notably, the synthesis of this type of bis(imidazolium) [1_4]cyclophanes has exploited their ability to bind chloride anions and permitted the examination of anion templates within simple bis(imidazolium) systems.[5,17,18] Finally, hydrophobic systems can be represented by dicationic calix[4]arenes **6**·2Br[19] and **7**·2Br.

The chloride-for-anion swap of the open-chain compounds **2**·2Cl and **3**·2Cl was first examined in methanol by using the AER (A^- form) conveniently loaded with assorted anions and the resulting compounds **2**·2A and **3**·2A were obtained in yields ranging from 28 to 100%. Due to the low solubility of several ion pairs in methanol, especially for the PF_6^- counteranion, and subsequent yields of less than 95%, methanol was changed for the more lipophilic solvent mixture CH_3CN/CH_3OH (9:1), which gave nearly quantitative yields (Scheme 2 and Table 1). By using our standard method in methanol, the anion detection reagent **4**·2Br provided the ion pairs **4**·2AcO or **4**·2CH_3SO_3 in quantitative yields. The effectiveness of the method was further confirmed by the excellent cleanup result, affording free-halide ion pairs and a bromide content of <13 ppm (Table 1). Following the AER (A^- form) method in methanol, the bis(imidazolium)-cyclophane **5a**·2Cl was passed through a column packed with an AER loaded with the appropriate anion and transformed into pure **5a**·2A in quantitative yield, except for **5a**·PF_6 (Scheme 2 and Table 1).

The magic hexafluorophosphate counteranion together with the tetrafluoroborate ion offer the possibility of examining weakly coordinating and charge-diffused anions.[4] The transformation of **5a**·2Cl into **5a**·2PF_6 proceeded in only a moderate yield of 63% due to the low solubility of the resulting hexafluorophosphate dication in methanol, whereas the low solubility of the starting ion pair **5a**·2Cl in acetonitrile hampered counteranion exchange. The chloride-for-hexafluorophosphate swap was then carried out in CH_3CN/CH_3OH (9:1), yielding 95% of pure chloride-free **5a**·PF_6 with <6 ppm Cl^-. The less polar bis(imidazolium)-calix[4]arenes **6**·2Br and **7**·2Br were directly assayed in acetonitrile and the bromide ion was swapped for several anions in excellent yields (Scheme 2 and Table 1).



Scheme 2. Swapping a halide ion for different anions of bis(imidazolium) anion receptors and sensors **2·2Cl**–**7·2Br**: Testing the AER (A^- form) method in organic solvents. Bz = benzoyl.

Scope and Limitations of the AER (A^- Form) Method

When applied to known imidazolium-based systems for anion recognition, for example, **1**·Cl–**7**·2Br, counteranion

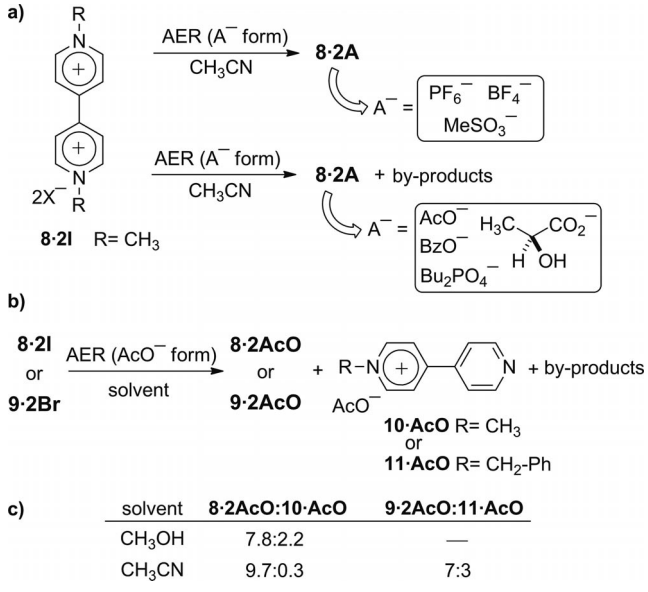
Table 1. Counteranion exchange (% yield of the recovered new ion pair; n.t. = not tested)[a] in bis(imidazolium) salts **2**·2Cl–**7**·2Br by using the AER (A^- form) method in CH_3OH, CH_3CN and CH_3CN/CH_3OH (9:1).

Anion	**2**·2Cl CH_3OH	CH_3CN[b]	**3**·2Cl CH_3OH	CH_3CN[b]	**4**·2Br CH_3OH	CH_3CN	**5**·2Cl CH_3OH	CH_3CN	**6**·2Br CH_3CN	**7**·2Br CH_3CN
AcO^-	70	100	100	–	99	–	95	–	100	100
BzO^-	100	–	100	–	n.t.	–	100	–	90	100
(*S*)-Lactate$^-$	100	–	95	–	n.t.	–	100	–	n.t.	n.t.
$Bu_2PO_4^-$	96	–	85	100	89	98	100	–	90	98
$MeSO_3^-$	42	100	80	100	100	–	100	–	100	100
BF_4^-	91	100	79	97	n.t.	–	100	–	n.t.	n.t.
PF_6^-	32	95	28	98	86	98	63	95[b]	95	97
$CF_3SO_3^-$	100	–	87	100	76	100	100	–	n.t.	n.t.

[a] Yields ≥ 95% in CH_3OH were not further investigated. Halide contents after anion exchange were <6 ppm of Cl^- or <13 ppm of Br^- determined by silver chromate test; 0.011 mL of $AgNO_3$ aqueous solution is enough to react with nearly 6 ppm (mg L^{-1}) of chloride anion or 13 ppm (mg L^{-1}) of bromide anion. [b] In CH_3CN/CH_3OH (9:1).

exchange proceeded in excellent to quantitative yields and confirmed the versatility and benefits of the AER (A^- form) method in organic solvents with a range of polarities. The most appropriate solvent or solvent mixture was chosen according to the hydrophobic nature of both the cation and the counteranion species. A limiting factor of this counteranion exchange method, however, concerns the chemical stability of the cationic and oligocationic systems in basic media. The basicity of the counteranions[10,11] could modulate the chemical response of the resulting ion pairs, although this is not a restriction of the AER (A^- form) method itself.

A brief study was then centered on the versatility of the AER (A^- form) method when applied to known building blocks, such as *N*,*N*-disubstituted-4,4′-bipyridinium salts, methyl viologen (MV) **8**·2I,[21,22] and **9**·2Br.[22,23] These compounds provided simple models to examine their chemical response under the conditions of the counteranion exchange protocol, which makes use of a strong basic anion exchange resin in the A^- form in organic solvents (Scheme 3 and Table S1 in the Supporting Information). The instability of N,N-disubstituted viologens under basic conditions is noteworthy.[24,25] Moreover, habitual components of molecular machines, like Stoddart's classic blue box, contain the dicationic *N*-benzyl-4,4′-bipyridinium structural motif, which in turn has a recognized susceptibility to alteration and decomposition under basic conditions.[26]



Scheme 3. Application of the AER (A^- form) method to 4,4′-bipyridinium salts. (a) Transformation of **8**·2I and **9**·2Br into **8**·2A and **9**·2A, respectively. (b) Chemical response of 1,1′-dimethylviologens **8**·2AcO and **9**·2AcO in methanol or acetonitrile. (c) Dications **8**·2AcO and **9**·2AcO and the ratio of the cationic counterparts **10**·AcO and **11**·AcO.

The *N*,*N*-dimethyl-4,4′-bipyridinium **8**·2I and especially the **9**·2Br *N*,*N*′-dibenzyl-4,4′-bipyridinium salt provide challenges when carrying out the halide-for-anion swap using strongly basic anion-exchange resins. Herein, the resin Amberlyst A-26 was chosen, but other strongly basic anion-exchange resins could be used instead. Due to the low solubility of dimethylviologen **8**·2I in methanol and the prospect of decreased solubility of the resulting ion pair, **8**·2A, anion exchange was carried out directly in acetonitrile.

The AER (A^- form) method functioned with weakly basic anions, such as PF_6^-, BF_4^-, and $MeSO_3^-$, and the corresponding dimethylviologens **8**·2A were stable (Scheme 3 and Table S3 in the Supporting Information). Thus, anion exchange proceeded in yields from 83 to 100%, depending on the solubility of the ion pair in acetonitrile, but the use of less polar solvent mixtures was not tested. The **8**·2PF_6, **8**·2BF_4 and **8**·2$MeSO_3$ electrospray ionization mass spectra in the negative mode [ESI(–)-MS] exhibited the absence of the iodide counteranion, confirmed by the chromate test, and showed clean ^{1}H NMR spectra.

The AER (A^- form) method stopped working when the iodide counteranion was exchanged with carboxylate ions, such as AcO^-, BzO^-, or (*S*)-lactate$^-$. Simple 4,4′-bipyridinium salts **8**·2RCO_2 were obtained together with alteration and decomposition byproducts. Similar chemical instability was observed for viologen **8**·2Bu_2PO_4, due to the proclivity of the 4,4′-bipyridinium salts **8**·2A to alteration and decomposition, according to the basicity of the counteranion. Thus, the *N*,*N*-dimethyl-4,4′-bipyridinium acetate **8**·2AcO was quite unstable and the propensity to be transformed into the dealkylated cation **10**·AcO together with alteration and decomposition byproducts was even stronger for the *N*,*N*′-dibenzyl-4,4′-bipyridinium salt **9**·2AcO (Scheme 3); this was not further studied.

Characterization by Spectroscopic Methods

The structure of the imidazolium salts **1**·2A, the bis(imidazolium) systems **2**·2A–**7**·2A, and the dicationic 4,4′-bipyridinium salts **8**·2A and **9**·2Br were confirmed mainly by ^{1}H NMR spectroscopy and when necessary unambiguous assignments were made by NOE difference experiments at 400 MHz (Tables S4 to S6 and Figure S1 in the Supporting Information). Moreover, the amount of halide content was determined by a silver chromate test, following a similar protocol to that described by Sheldon and co-workers.[27] Additionally, Clare et al. have demonstrated that the use of alumina and silica columns can leave a low level of residual particulate contamination in ILs.[9,28] Consequently, nanoparticulates may also be an issue when using strongly basic anion-exchange resins (A^- form), but analysis of possible particulate contamination is beyond the scope of the present study.

Electrospray Ionization Mass Spectrometry

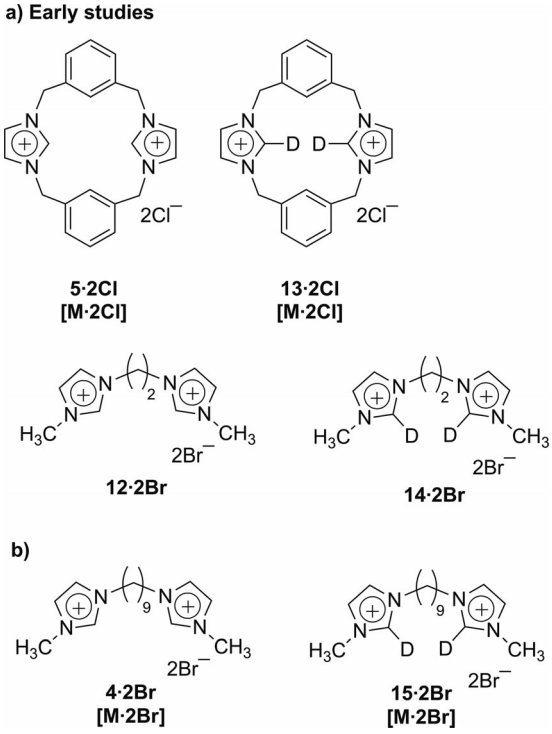
ESI-MS is a consolidated technique that bridges gas- and solution-phase chemistry and has been utilized in supramolecular chemistry since the 1990s. Thus, for the characterization of tetracationic catenanes, at both the molecular and supramolecular level, Stoddart and co-workers reported that ESI(+)-MS was better than other soft-ioniza-

tion MS techniques, such as FAB-MS.[29] Since 2000, we have examined the gas-phase response of bis(imidazolium) systems such as [1$_n$]*meta*-cyclophanes, for example, **5**·2Cl, protophanes, and calix[4]arenes.[5,17–19,30,31] ESI(+)-MS analysis was then applied to characterize bis(imidazolium)-based precursors for N-heterocyclic carbene ligands,[32] and to investigate the gas-phase behavior of imidazolium ionic liquids.[33] By taking further advantage of the ESI-MS technique, ILs have been analyzed,[8,33–35] including the application of an oligocationic ion-pairing reagent for anion detection of **4**·2Br (M·2Br).[16] Thus, ESI(+)-MS/MS experiments improved sensitivity and selectivity for the corresponding complexed species **4**·2A and the proposed fragmentation pathways of the singly charged ion $[M + A]^+$ include the formation of singly charged carbene species $[M - H]^+$.[16a,35]

The earliest examples derived from simple bis(imidazolium)-based frameworks include the known cyclophane **5**·2Cl[17] and the open-chain precursor for N-heterocyclic carbene ligands, **14**·2Br,[36] which merits a brief comment. Electrosprayed **5**·2Cl and **12**·2Br produced loss of the counteranions and fission of the labile imidazolium $(C–H)^+$ bond. The three common ions were $[M]^{2+}$, $[M + Cl]^+$, and the imidazolylidene species $[M – H]^+$; hence, direct ESI-MS evidence was obtained for singly charged carbene ions $[M – H]^+$ and this representative peak appeared in the ESI mass spectra of the regiospecific deuterated counterparts **13**·2Cl and **14**·2Br as the singly charged ion $[M – D]^+$, which validated the positive-ion mode ESI(+)-MS study (Scheme 4). Cyclophane **5**·2Cl gave clean ESI(+) mass spectra and changing the nature of the bis(imidazolium) framework to the open-chain bis(imidazolium) model **12**·2Br produced a different ESI(+) response, with the appearance of several peaks due to fragmentation of the dicationic moiety, although it still gave the three characteristic peaks with variable relative abundance.[18] Moreover, positive-ion mode ESI tandem mass spectrometry (ESI-MS/MS) of dication **5**·2Cl showed the formation pathway of the carbene species (Scheme S1 in the Supporting Information).[31]

The present brief ESI(+)-MS study focuses on the **5**·2Cl prototype; the open-chain compound **4**·2Br; and its regiospecific counterpart **15**·2Br, which is deuterated on the acidic imidazolium C(2)–H to corroborate the ESI(+) evidence of the imidazolylidene ions: $[M – H]^+$ or $[M – D]^+$. Their gas-phase response is discussed from data gained by ESI(+)-MS experiments (see Exp. Sect.).

Under conditions of 75 V cone voltage (V_c), which was the minimum V_c necessary for an adequate ion intensity of **4**·2Br, the base peak corresponded in each case to the $[M]^{2+}$ ion. Yet when the V_c was increased to 215 V, cyclophane **5**·2Cl gave the doubly charged ion $[M]^{2+}$ as the base peak and the imidazolylidene ions $[M – H]^+$ with a relative abundance of 49%. Whereas at 215 V, the ESI(+) response of the open-chain pairs **4**·2Br and **15**·2Br resulted in the appearance of several peaks due to fragmentation of the bis(imidazolium) dication, although they still gave the $[M]^{2+}$ and $[M – H]^+$ or $[M – D]^+$ species in about 11 and 6%, respectively. Thus, the base peak of the open-chain compound pair corresponded to the singly charged fragment at *m*/*z* 207 and 208, respectively, which may be attributed to the corresponding cationic imidazolium olefin, due to a type of β elimination in the gas phase (Table 2 and Figures S2 to S4 in the Supporting Information). It should be recalled that, in the solution phase, the tendency to un-



Scheme 4. A comparative ESI(+)-MS study of **5**·2Cl, the open-chain system **4**·2Br, and its regiospecific deuterated counterpart **15**·2Br. (a) Early studies: ESI(+) response of **5**·2Cl, **12**·2Br, and their regiospecific deuterated counterparts **13**·2Cl, **14**·2Br (ref.[18,31]). (b) Bis(imidazolium) open-chain **4**·2Br and its regiospecific deuterated counterpart **15**·2Br (Figures S3 and S4 in the Supporting Information).

Table 2. Positive-ion ESI-MS of **4**·2Br, **5**·2Cl, and the deuterated counterpart **15**·2Br.[a,b]

Compound (MW)	V_c [V]	Ions, *m*/*z* ratio relative abundance [%] $[M]^{2+}$	$[M – H]^+$	$[M – D]^+$	$[M + X]^+$
5·2Cl (412.122)		171.092	341.176	–	377.153
	75	100	[c]		5
	215	100	49		3
4·2Br (450.082)[d]		145.137	289.266	–	370.178
	75[e]	100	[c]		1
	215[f,g]	13	8		7
15·2Br (452.094)[d]		146.143	–	290.272	372.190
	75[e]	100		[c]	3
	215[f,h]	10		3	3

[a] Molecular weight (MW) and ion *m*/*z* values apply to the lowest mass component of any isotope distribution and are based on a scale in which $^{12}C = 12.000$. [b] In CH_3CN/H_2O (1:1, v/v). [c] No signal observed. [d] Atomic weight of bromine is the average of the mass component of the isotope distribution. [e] The minimal cone voltage where signal abundance remains adequate. [f] Fragment ion: 1-methyl-3-(non-8-enyl)imidazolium. [g] Fragment ion at *m*/*z* = 207.185 (100%). [h] Fragment ion at *m*/*z* = 208.191 (100%).

dergo a type of β elimination was examined with a set of quaternary heteroaromatic salts and exploiting this propensity toward β elimination allowed the synthesis of 2-vinyl benzimidazoles monomers.[37] Hence, the nature of the bis(imidazolium) frameworks modulated the relative stability of the ESI(+) characteristic peaks in accordance with our previous ESI(+)-MS and ESI(+)-MS/MS studies of different bis(imidazolium)-based frameworks, such as the compound pairs **5**·2Cl, **12**·2Br and **13**·2Cl, **14**·2Br.[5,17c,18,31]

Conclusions

Out of the variety of quaternary imidazolium salts, the present study selected several examples of cationic and dicationic systems that could allow the halide-to-anion switch to be assessed by an AER (A^- form) in nonaqueous media. Depending on the hydrophobic nature of the quaternary salts, counteranion exchange was carried out in organic solvents and solvent mixtures with variable polarity and progressed in excellent to quantitative yields. Analysis of the gas-phase response of bis(imidazolium) frameworks, past and present, by ESI(+)-MS gave great insight into the reported results. The ESI(+) mass spectra of bis(imidazolium) systems such as the cyclophane prototype **5**·2Cl, the open-chain **4**·2Br, and its deuterated counterpart **15**·2Br showed that the nature of the framework modulated their ESI response.

On the whole, the AER (A^- form) method is simple, but not trivial, and can be considered the method of choice for counteranion exchange in a wide array of imidazolium systems. It could also be suitable for elaborate charged molecular architectures with specific physical and/or biological properties. The performance of this method can be developed in fields that include anion complexation chemistry and ILs.

Experimental Section

General: ^{1}H NMR spectra were recorded on Varian Gemini 300 (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) and Mercury 400 (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) spectrometers at 298 K. ^{1}H and ^{13}C NMR chemical shifts were referenced to tetramethylsilane (TMS) as an internal reference. NOE difference experiments were recorded on a Mercury 400 spectrometer. The pH was measured with a benchmeter pH1100 (Eutech Instruments), using a Hamilton Flushtrode pH electrode for hydroalcoholic solutions. Starting materials were purchased from commercial suppliers and were used without further purification. All solvents were reagent grade and methanol was distilled prior to use. Compounds **1**·Cl,[13] **2**·2Cl,[14a] **3**·2Cl,[15b] **4**·2Br,[16d] **5**·2Cl,[17] **6**·2Br,[19] **8**·2I,[21] and **9**·2Br[23] were prepared according to literature procedures.

Electrospray Ionization Mass Spectrometry: ESI(+)-MS analyses were performed on a LC/MSD-TOF (2006) mass spectrometer from Agilent Technologies. The electrospray source operated under the following instrumental conditions: capillary voltage: 4 KV, V_c (fragmentor): 75 and 215 V, gas temperature: 300 °C, nebulizing gas: N_2 (pressure: 15 psi) and drying gas: N_2 (flow: 7.0 L min^{-1}). The eluent flowing through the probe was H_2O/CH_3CN (1:1, v/v) at flow rate 200 μL min^{-1}. Sample (μL) was introduced into the source with an HPLC system (Agilent 1100).

5,17-Bis(3-decyl-1-imidazolium)-25,26,27,28-tetrapropoxycalix[4]-arene Dibromide (7·2Br): A solution of 5,17-bis(imidazol-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene[19] (0.300 g, 0.413 mmol) in 1-bromodecane (5 mL) was heated to reflux for 16 h, under an argon atmosphere. A light brown solid was collected by filtration and washed with several portions of diethyl ether (3 × 10 mL) to give **4**·2Br (0.402 g, 83%). M.p. 268–270 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.28 (s, 2 H, Im), 8.20 (s, 2 H, Im), 7.27 (d, 4 H, $H_{10,12,22,24}$), 7.16 (t, 2 H, $H_{11,23}$), 6.68 (s, 2 H, Im), 6.53 (s, 4 H, $H_{4,6,16,18}$), 4.49–4.54 (m, 8 H, H_{ax} and N-CH_2-), 4.05 (t, 4 H, O-CH_2), 3.70 (t, 4 H, O-CH_2), 3.25 (d, 4 H, H_{eq}), 1.87–1.99 (m, 8 H), 1.74 (m, 4 H), 1.21 (m, 28 H), 1.12 (t, 6 H), 0.86 (t, 6 H), 0.91 (t, 6 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.9, 137.1, 135.4, 134.0, 129.9, 128.9, 124.8, 124.1, 120.0, 118.9, 77.7, 76.9, 50.4, 31.9, 31.1, 30.7, 29.5, 29.3, 29.2, 26.3, 23.5, 23.0, 22.8, 14.2, 10.8, 9.9 ppm. HRMS (ESI$^+$): calcd. for $C_{66}H_{94}N_4O_4$ $[M]^{2+}$ 503.3632; found 503.3620.

Bis(imidazolium) Salt 15a·2Br: Deuterium Exchange: A stirred solution of **4a**·2Br (0.134 g, 0.30 mmol) in D_2O (5 mL) under argon was maintained in a bath at 50 °C for 48 h. The reaction mixture was evaporated to dryness to afford **15a**·2Br (0.135 g, quantitative yield) as a colorless oil at room temperature. ^{1}H NMR (300 MHz, D_2O): δ = 1.31 (m, 10 H), 1.88 (m, 4 H), 3.91 (s, 6 H, N-CH_3), 4.20 (t, 4 H, N-CH_2-), 7.44 (d, 2 H), 7.49 (d, 2 H) ppm.

General Procedure to Load the AER [Resin (OH^- Form)] with Acids or Ammonium Salts: A glass column (1 cm diameter) packed with 2.5 g (ca. 3 cm^3) of commercially wet strongly basic anion exchange Amberlyst A-26 (OH^- form) was washed with water and the column bed was equilibrated progressively with water/solvent mixtures until reaching the selected solvent media used afterwards for anion loading (ca. 25 mL of each solvent mixture). A 1% acid or ammonium salt solution in the appropriate solvent was passed slowly through the resin until the eluates had the same pH value as the originally selected acid solution and then the resin was washed generously with solvent until constant pH. The process was carried out at room temperature by using gravity as the driving force.

General Procedure for Anion Exchange: A solution of the imidazolium salt (50–60 mM) in the selected solvent (10 mL) was passed slowly through a column packed with about 3 cm^3 of Amberlyst A-26 (A^- form) and then washed with solvent (25 mL). The combined eluates were evaporated and the residue obtained was dried in a vacuum oven at 60 °C with P_2O_5 and KOH pellets. The halide content was determined by the silver chromate test.[1,27]

It should be pointed out that Clare et al. demonstrated that the use of alumina and silica columns could leave a low level of residual particulate contamination in ILs.[28] Consequently, nanoparticulates may also be an issue when using strongly basic AERs (A^- form), but the analysis of possible particulate contamination was out of the scope of the present study.

Supporting Information (see footnote on the first page of this article): Counteranion exchange, ^{1}H NMR spectra, and ESI(+)-MS results.

Acknowledgments

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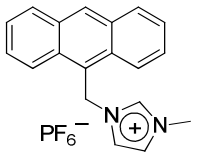
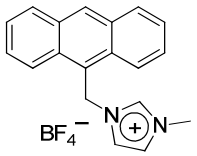
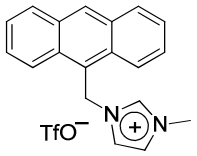
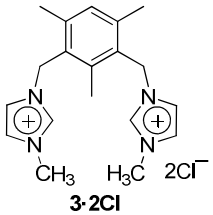
SUPPORTING INFORMATION

DOI: 10.1002/ejoc.201101355
Title: A Halide-for-Anion Swap Using an Anion-Exchange Resin (A^- Form) Method: Revisiting Imidazolium-Based Anion Receptors and Sensors
Author(s): Ermitas Alcalde,* Neus Mesquida,* Anna Ibáñez, Immaculada Dinarès

Table S1. Classical counteranion exchange versus the AER (A^- form) method applied to:
(i) fluorogenic anion sensor (anthrylmethyl)imidazolium chloride **1·Cl**;
(ii) open chain bis(imidazolium) systems **3·Cl** and **4·2Br**;
(iii) bis(imidazolium) cyclophane anion receptor prototype **5·2Cl**;
(iv) *N,N*-disubstituted viologen **8·2I**.

Compound	Reference		Our protocol
 **1·PF_6**	Ref 13	**1·Cl→1·PF_6** 89% A mixture of **1·Cl** and KPF_6 in water (15 mL) was stirred at room temperature in the dark for 4 h. The reaction mixture was then filtered and the solid product was washed with water and air dried.	[Cl]→[PF_6] 70% CH_3OH [Cl]→[PF_6] 98% CH_3CN:CH_3OH (9:1)
 **1·BF_4**	Ref 13	**1·Cl→1·BF_4** 70% A mixture of **1·Cl** and $NaBF_4$ in acetone was stirred at room temperature in the dark for 24 h. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The solid obtained was dissolved in dichloromethane and stored at –22ºC for 24 h. After filtration the solvent was removed.	[Cl]→[BF_4] 78% CH_3OH [Cl]→[BF_4] 100% CH_3CN:CH_3OH (9:1)
 **1·TfO**	Ref 13	**1·Cl→1·TfO** 72% A mixture of **1·Cl** and $LiSO_3CF_3$ in dichloromethane was stirred at room temperature in the dark for 24 h. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The solid obtained was dissolved in dichloromethane and stored at –22ºC for 24 h. After filtration the solvent was removed.	[Cl]→[TfO] 93% CH_3OH [Cl]→[TfO] 95% CH_3CN:CH_3OH (9:1)
 **3·2Cl**	Ref 15a	**3·2Br→3·2PF_6** (85%) The bromide salt was converted to its PF_6 salt by a metathesis reaction using KPF_6 in methanol and was obtained as white crystalline solid, in 85% yield after recrystallization from hot water.	[Cl]→[PF_6] 28% CH_3OH [Cl]→[PF_6] 98% CH_3CN:CH_3OH (9:1)

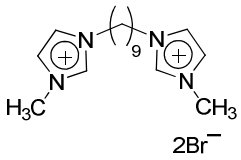
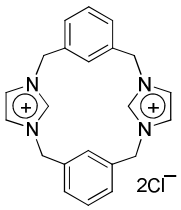
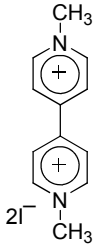
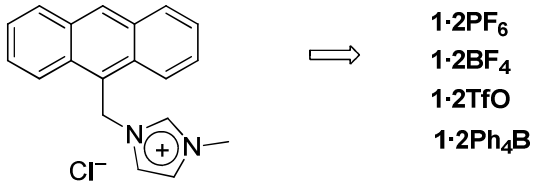
 **4·2Br**	Ref 16d	**4·2Br → 4·2PF$_6$** (yield= No data) To ~10 grams of the bromide salt in 150 mL water, two molar equivalents of HPF_6 were added slowly with stirring. The remaining ionic liquid was washed with water until all washings were no longer acidic and no trace of AgBr was observed using $AgNO_3$. The solid was filtered under vacuum and allowed to dry in an oven at 130 ºC for 4 days. After drying, they were then placed under a P_2O_5 vacuum.	[Br]→[PF_6] 86% CH_3OH [Br]→[PF_6] 98% CH_3CN
 **5·2Cl**	Ref 17, 18b	**5·2Cl → 5·2PF6** 91% Treatment of 3·2Cl with a strongly basic anion-exchange resin (OH– form) followed by immediate collection of the eluates in aq. HPF6 to pH = 3.	[Cl]→[PF6] 63% CH_3OH [Cl]→[PF6] 95% CH_3CN:CH_3OH (9:1)
 **8·2I**	Ref 21	**8·2I → 8·2PF6** 80% Paraquat diiodide (230 mg, 0.523 mmol) was dissolved in water (15 mL) and ammonium hexafluorophosphate (170 mg, 1.04 mmol) was added. The contents were warmed to obtain a clear solution and allowed to cool. The hexafluorophosphate salt crystallised out as pale yellow needles. Yield: 200 mg, 80%.	[I]→[PF6] 100% CH_3CN

Table S2 Classical counteranion exchange versus the AER (A^- form) method of (anthrylmethyl)imidazolium chloride **1·Cl**.[a]



1·2Cl

⟹

1·2PF$_6$
1·2BF$_4$
1·2TfO
1·2Ph$_4$B

	Protocol A (%)	**Protocol B** (%)	**Protocol C** (%)	**Protocol D**[b] (%)	**Protocol E**[b]
PF_6^-	89	57	70	98	—
BF_4^-	70	55	78	100	—
$CF_3SO_3^-$	72	—	93	95	—
Ph_4B^-	—	—	—	79	100

[a]Yield of the recovered new ion pair. [b]Halide contents after anion exchange determined by silver chromate test; 0.011 mL of $AgNO_3$ aqueous solution is enough to react with nearly 6 ppm ($mg \cdot L^{-1}$) of chloride anion.

Protocol A. Classical counteranion exchange (Table S1 and ref nº 13).

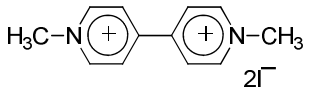
Protocol B. A methanolic solution of **1·2Cl** was passed through a column packed with an AER (OH^- form) and aqueous acid solution was then added to pH = 6. The precipitate was filtered and dried.

Protocol C. A methanolic solution of **1·2Cl** was passed through a column packed with an AER (A^- form), and the eluates were evaporated.

Protocol D. A CH_3CN:CH_3OH (9:1) solution of **1·2Cl** was passed through a column packed with an AER (A^- form), and the eluates were evaporated.

Protocol E. A CH_3CN:CH_3OH:CH_2Cl_2 (1.5:0.5:5) solution of **1·2Cl** was passed through a column packed with an AER (Ph_4B^- form), and the eluates were evaporated.

Table S3. Dicationic system **8·2I**. Counteranion swap using the AER (A^- form) method[a,b]

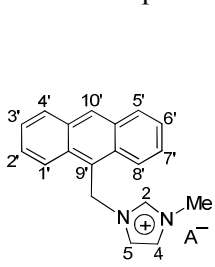


8·2I

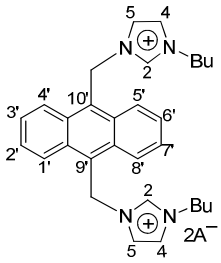
	8·2I
Anion	CH_3CN
$MeSO_3^-$	100
BF_4^-	83
PF_6^-	100

[a]Yield of the recovered new ion pair.
[b]Halide contents after anion exchange was < 20 ppm of I^- determined by silver chromate test.

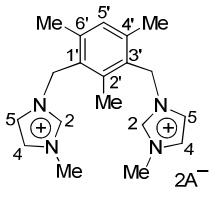
Table S4. Selected ^{1}H spectroscopic data of imidazolium salts **1·A**, **2·2A**, **3·2A** and **5·2A** at 300 MHz



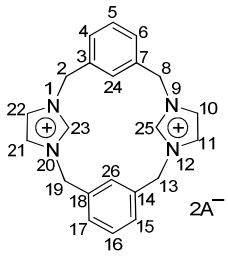
1·A



2·2A



3·2A

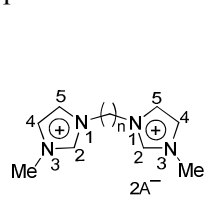


5·2A

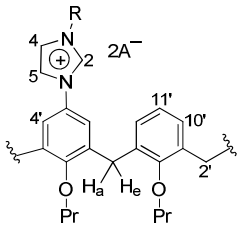
Compd.	Solvent	Conc. (M)	2-H[a]	4-H	5-H	–CH_2–	1'-H[b]	10'-H	24-H[c]
1·Cl[d]	CD_3CN	0.015	8.73	7.30	7.38	6.42	8.35	8.77	—
1·BF_4	CD_3CN	0.02	8.16	7.29	7.33	6.27	8.24	8.71	—
1·PF_6	CD_3CN	0.02	8.13	7.28	7.35	6.26	8.23	8.72	—
1·CF_3SO_3	CD_3CN	0.02	8.09	7.29	7.40	6.32	8.27	8.78	—
1·Ph_4B	CD_3CN	0.02	8.05	*e*	7.38	6.30	8.26	8.79	—
1·Ph_4B	CD_3CN/D_2O[f]	0.02	*g*	*e*	7.36	6.29	8.25	8.78	—
1·Ph_4B	CD_3CN/TFA[h]	0.02	8.00	*e*	7.36	6.28	8.26	8.79	—
1·Ph_4B	DMSO-d_6	0.02	8.80	7.66	7.72	6.47	8.46	8.85	
2·2Cl[d]	$CDCl_3$	0.02	9.38	7.05	8.90	6.57	7.80-7.78	—	—
2·2Cl	DMSO-d_6	0.02	9.24	7.68	7.81	6.60	8.61-8.57	—	—
2·2AcO	DMSO-d_6	0.02	9.53	7.61	7.77	6.61	8.63-8.59	—	—
2·2BzO	DMSO-d_6	0.02	9.28	7.61	7.77	6.60	8.63-8.59	—	—
2·2(*S*)-lactate	DMSO-d_6	0.02	9.21	7.59	7.78	6.59	8.62-8.58	—	—
2·2Bu_2PO_4	DMSO-d_6	0.02	9.29	7.58	7.78	6.60	8.63-8.59	—	—
2·2$MeSO_3$	DMSO-d_6	0.02	9.03	7.59	7.78	6.57	8.60-8.57	—	—
2·2BF_4	DMSO-d_6	0.02	9.00	7.58	7.77	6.56	8.59-8.56	—	—
2·2PF_6	DMSO-d_6	0.02	9.01	7.58	7.77	6.56	8.59-8.56	—	—
2·2CF_3SO_3	DMSO-d_6	0.02	9.01	7.59	7.77	6.57	8.60-8.57	—	—
3·2Cl	DMSO-d_6	0.04	9.21	7.76	7.76	5.47	—	—	—
3·2AcO	DMSO-d_6	0.04	9.49	7.73	7.73	5.47	—	—	—
3·2BzO	DMSO-d_6	0.04	9.23	7.73	7.69	5.47	—	—	—
3·2(*S*)-lactate	DMSO-d_6	0.04	9.06	7.74	7.68	5.47	—	—	—
3·2Bu_2PO_4	DMSO-d_6	0.04	9.17	7.75	7.71	5.47	—	—	—
3·2$MeSO_3$	DMSO-d_6	0.04	8.82	7.32	7.64	5.45	—	—	—
3·2BF_4	DMSO-d_6	0.04	8.76	7.72	7.62	5.44	—	—	—
3·2PF_6[d]	DMSO-d_6	0.04	8.75	7.71	7.61	5.44	—	—	—
3·2CF_3SO_3	DMSO-d_6	0.04	8.77	7.71	7.62	5.44	—	—	—
5·2Cl	DMSO-d_6	0.02	9.88	7.85	7.85	5.44	—	—	7.47
5·2Cl[i]	DMSO-d_6	0.0015	9.40	7.82	7.82	5.43	—	—	7.08
5·2AcO	DMSO-d_6	0.014	10.69	7.77	7.77	5.41	—	—	7.77
5·2BzO	DMSO-d_6	0.012	10.39	7.78	7.78	5.42	—	—	7.63
5·2(*S*)-lactate	DMSO-d_6	0.02	9.74	7.79	7.79	5.43	—	—	7.23
5·2Bu_2PO_4	DMSO-d_6	0.02	10.41	7.76	7.76	5.40	—	—	7.67
5·2$MeSO_3$	DMSO-d_6	0.02	9.39	7.81	7.81	5.43	—	—	7.10
5·2BF_4	DMSO-d_6	0.02	9.60	7.82	7.82	5.43	—	—	7.26
5·2PF_6	DMSO-d_6	0.02	9.27	7.75	7.75	5.43	—	—	6.97
5·2CF_3SO_3	DMSO-d_6	0.02	9.23	7.82	7.82	5.43	—	—	6.93

[a]The equivalent proton atoms are abbreviated as follows: *2-H* = 23,25-H for **5·2A**. [b]The equivalent proton atoms are abbreviated as follows: *1'-H* = 1',8'-H for **1·A** and *1'-H* = 1',4',5',8'-H for **2·2A**. [c]The equivalent proton atoms are abbreviated as follows: *24-H* = 24,25-H for **5·2A**. [d]Assignation of signals by NOE at 400 MHz (see Figure S1). [e]Signal not observed. [f]D_2O (*ca.* 0.011ml) was added. [g]Signal not observed due to H/D exchange. [h]TFA (*ca.* 0.011ml) was added. [i]The NMR spectroscopic data are in accordance with those reported in literature (see ref. 18b).

Table S5. Selected ^{1}H spectroscopic data of imidazolium salts **4·2A**, **6·2A** and **7·2A** at 300 MHz



4·2A n = 9

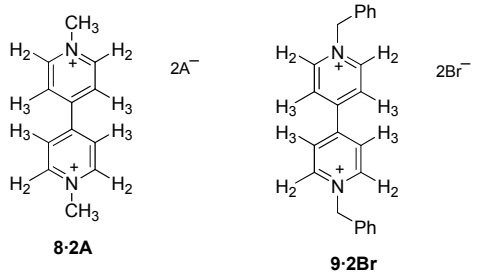


6·2A R = –C_4H_9
7·2A R = –$C_{10}H_{21}$

Compd.	Solvent	Conc. (M)	2-H	4-H	5-H	–CH_2–[a]	–CH_2–[b]	4'-H	10'-H	11'-H
4·2Br[c]	DMSO-d_6	0.02	9.15	7.70	7.77	4.14	—	—	—	—
4·2AcO	DMSO-d_6	0.02	9.55	7.72	7.79	4.16	—	—	—	—
4·2Bu$_2$PO$_4$	DMSO-d_6	0.02	9.40	7.73	7.80	4.16	—	—	—	—
4·2MeSO$_3$	DMSO-d_6	0.02	9.14	7.71	7.77	4.15	—	—	—	—
4·2PF$_6$	DMSO-d_6	0.02	9.08	7.69	7.74	4.14	—	—	—	—
4·2CF$_3$SO$_3$	DMSO-d_6	0.02	9.08	7.70	7.75	4.14	—	—	—	—
6·2Br	DMSO-d_6	0.01	9.86	8.28	8.03	—	3.32, 4.43	7.62	6.36	6.36
6·2AcO	DMSO-d_6	0.01	10.18	8.29	8.04	—	3.32, 4.42	7.64	6.40	6.32
6·2BzO	DMSO-d_6	0.01	10.16	8.29	8.04	—	3.30, 4.41	7.63	6.40	6.31
6·2Bu$_2$PO$_4$	DMSO-d_6	0.01	10.16	8.32	8.04	—	3.33, 4.42	7.66	6.38	6.31
6·2MeSO$_3$	DMSO-d_6	0.01	9.82	8.27	8.02	—	3.32, 4.45	7.60	6.39	6.31
6·2PF$_6$[d]	DMSO-d_6	0.01	9.79	8.26	8.01	—	3.31, 4.43	7.60	6.38	6.32
7·2Br	DMSO-d_6	0.01	9.87	8.28	8.03	—	3.32, 4.43	7.61	6.39	6.31
7·2AcO	DMSO-d_6	0.01	10.24	8.28	8.03	—	3.31, 4.42	7.64	6.41	6.34
7·2BzO	DMSO-d_6	0.01	10.26	8.28	8.04	—	3.30, 4.41	7.63	6.42	6.30
7·2Bu$_2$PO$_4$	DMSO-d_6	0.01	10.14	8.30	8.04	—	3.32, 4.42	7.65	6.39	6.31
7·2MeSO$_3$	DMSO-d_6	0.01	9.80	8.56	8.03	—	3.31, 4.43	7.59	6.37	6.34
7·2PF$_6$	DMSO-d_6	0.01	9.79	8.26	8.01	—	3.32, 4.41	7.59	6.37	6.32

[a]Only -CH_2-Im^+ was indicated for **4·2A**. [b]The proton atoms are abbreviated as follows: -CH_2- = H_a, H_e for **6·2A** and **7·2A**. [c]Assignation of signals by NOE at 400 MHz (see Figure S1). [d]Assignation of signals by ROESY at 400 MHz (see Figure S1).

Table S6. Selected ^{1}H NMR data of 4,4'-bipyridinium salts **8·2A** and **9·2Br** at 300 MHz



Compound	Solvent	Conc (M)	H-2	H-3	–CH_3	–CH_2–
8·2I	DMSO-d_6	0.02	9.29	8.77	4.44	—
8·2MeSO$_3$	DMSO-d_6	0.02	9.29	8.78	4.45	—
8·2BF$_4$	DMSO-d_6	0.02	9.27	8.74	4.43	—
8·2PF$_6$	DMSO-d_6	0.02	9.27	8.74	4.43	—
9·2Br	DMSO-d_6	0.02	9.56	8.77	—	5.98

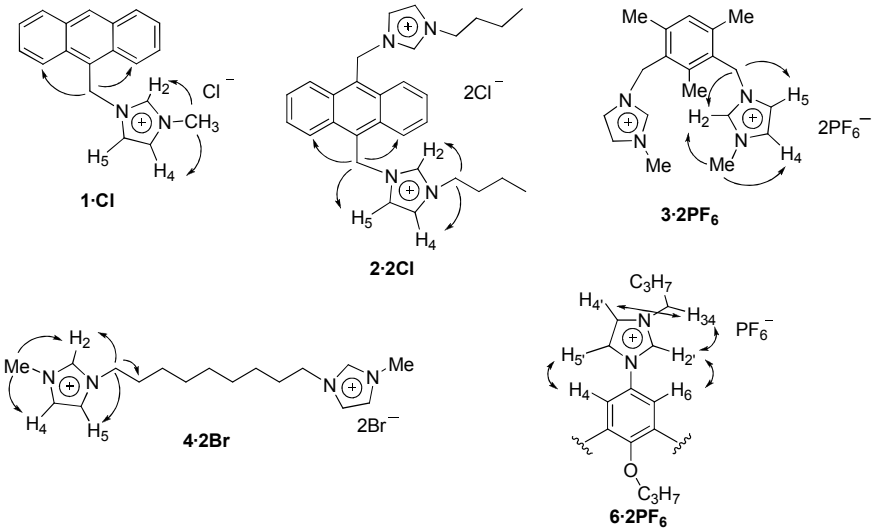
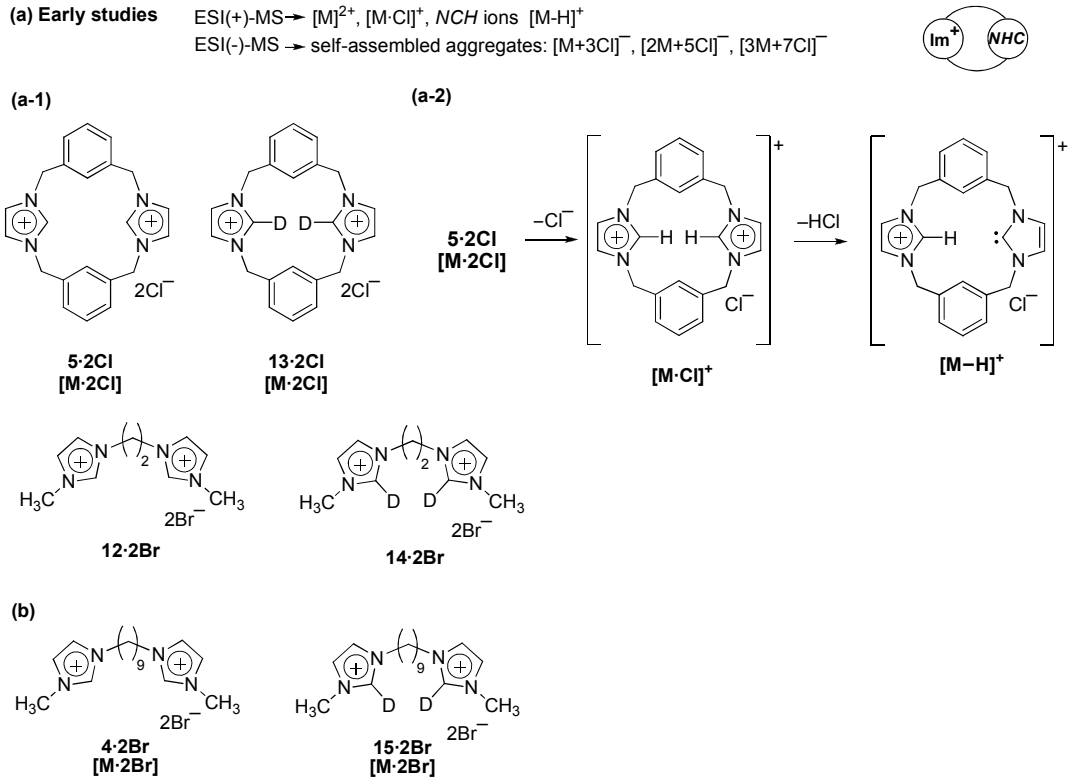
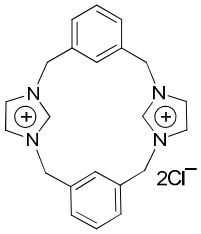


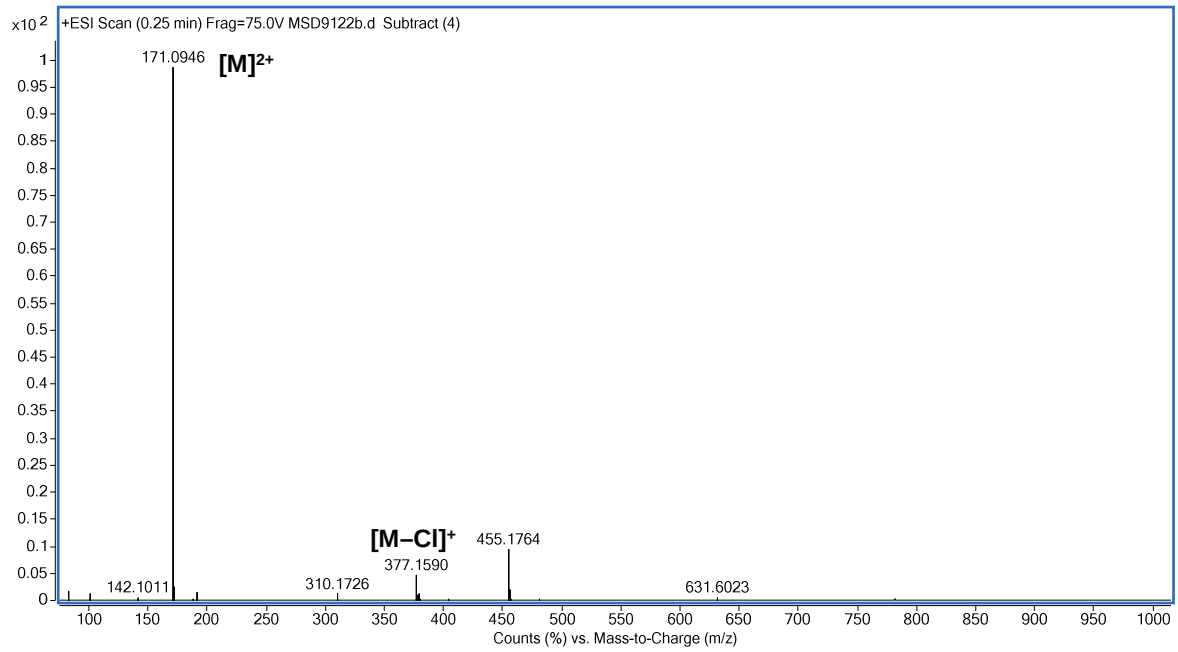
Figure S1. Key NMR responses for imidazolium salts **1·Cl**, **2·2Cl**, **3·2PF$_6$**, **4·2Br** and **6·2PF$_6$**: NOE difference experiments.



Scheme S1. ESI(+)-MS study of bis(imidazolium) cyclophane **5·2Cl**, the open-chain system **4·2Br** and its regiospecific deuterated counterpart **15·2Br** revealed direct singly charged carbene ions $[M - H]^+$ and $[M - D]^+$. (a) Early studies with bis(imidazolium)-based frameworks: (a-1) ESI(+) response of **5·2Cl**, **12·2Br** and their regiospecific deuterated counterparts **13·2Cl**, **14·2Br** (ref 18); (a-2) formation pathway of the imidazolylidene ions (refs 17c,31). (b) Bis(imidazolium) open-chain **4·2Br** and its regiospecific deuterated counterpart **15·2Br** (see Figures S3 and S4).



5·2Cl



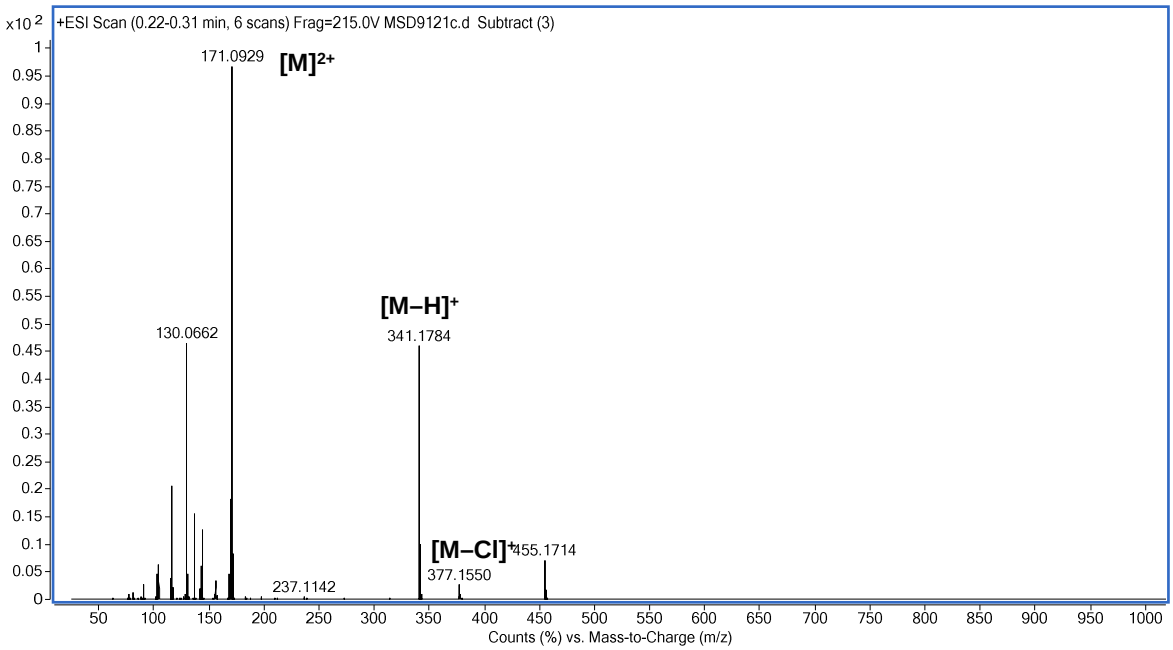
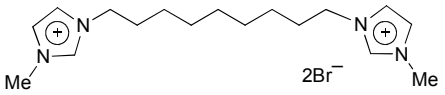
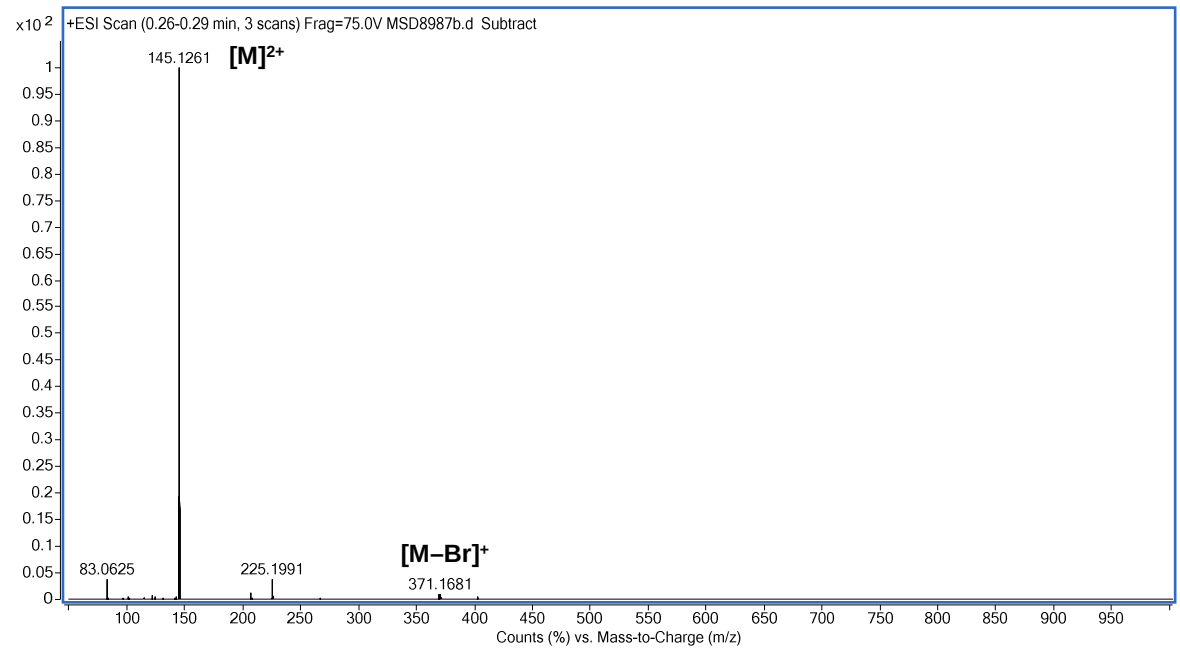


Figure S2. Positive-ion ESI mass spectra of **5·2Cl** sprayed from a 1:1 (v/v) mixture of CH_3CN:H_2O. Cone voltages: 75V and 215V.



4·2Br



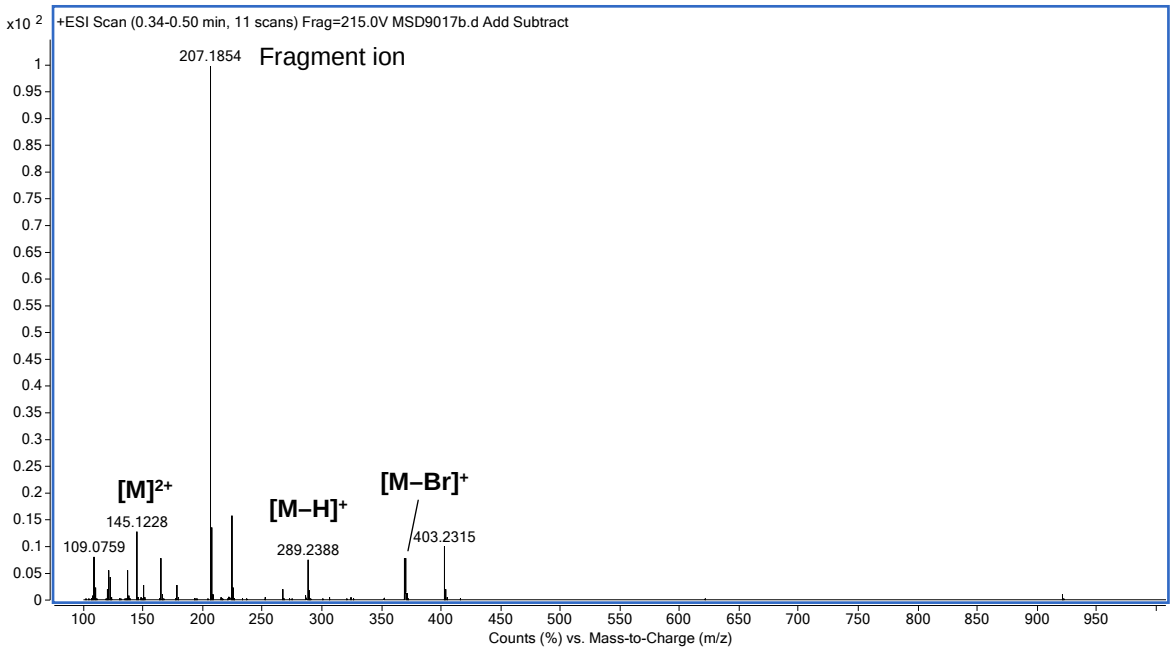
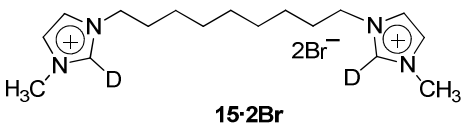
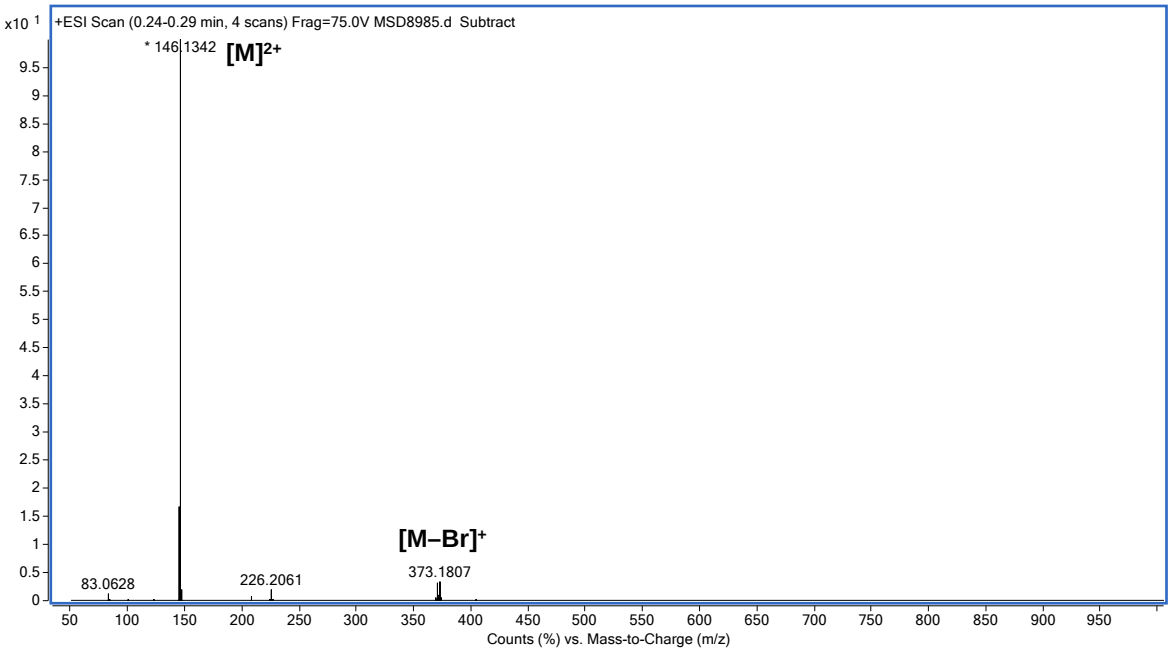


Figure S3. Positive-ion ESI mass spectra of **4·2Br** sprayed from a 1:1 (v/v) mixture of CH_3CN:H_2O. Cone voltages: 75V and 215V.



15·2Br



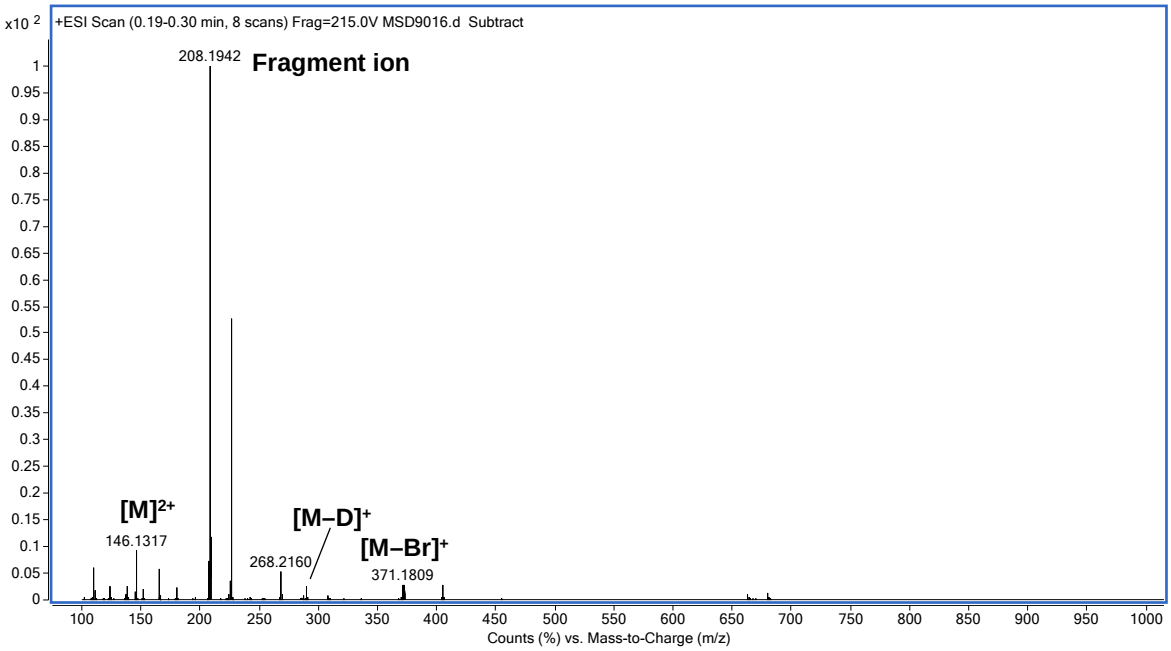


Figure S4. Positive-ion ESI mass spectra of **15·2Br** sprayed from a 1:1 (v/v) mixture of CH_3CN:H_2O. Cone voltages: 75V and 215V.

- **Azolium-based systems: application of an anion exchange resin (A^- form) method and ^1H NMR analysis of the charged-assisted $(C–H)^+\cdots$anion hydrogen bonds.**
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  (*pendent de publicació*).

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Article

Azolium-based systems: application of an anion exchange resin (A^- form) method and ^1H NMR analysis of the charged-assisted $(C–H)^+\cdots$anion hydrogen bonds†

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Abstract: The counteranion exchange of quaternary 1,2,3-triazolium salts was examined using a simple method that permitted halide ions to be exchanged for a variety of anions using a strong basic anion exchange resin (A^- form). The AER (OH^- form) loading was carried out using three different anion sources -acids, ammonium salts or sodium azide- in either methanol or a hydroalcoholic solution. The AER (A^- form) anion exchange method was then applied to 1,2,3-triazolium-based ionic liquids and the iodide-to-anion exchange in methanol proceeded in excellent to quantitative yields, concomitantly removing halide impurities. Additionally, a strong basic AER (N_3^- form) was used to obtain the benzyl azide component from benzyl halide under mild reaction conditions in the solvent mixture CH_3CN/CH_3OH (1:1). Following a similar protocol, bis(azidomethyl) arenes were also synthesized in excellent yields. The results of a proton NMR spectroscopic study of simple azolium-based ion pairs are discussed, with attention focused on the significance of the charged-assisted $(C–H)^+\cdots$anion hydrogen bonds of simple azolium systems such as 1-butyl-3-methylimidazolium and 1-benzyl-3-methyl-1,2,3-triazolium salts.

Keywords: imidazolium salts; 1,2,3-triazolium salts; anion exchange resin; hydrogen bonds; ionic liquids

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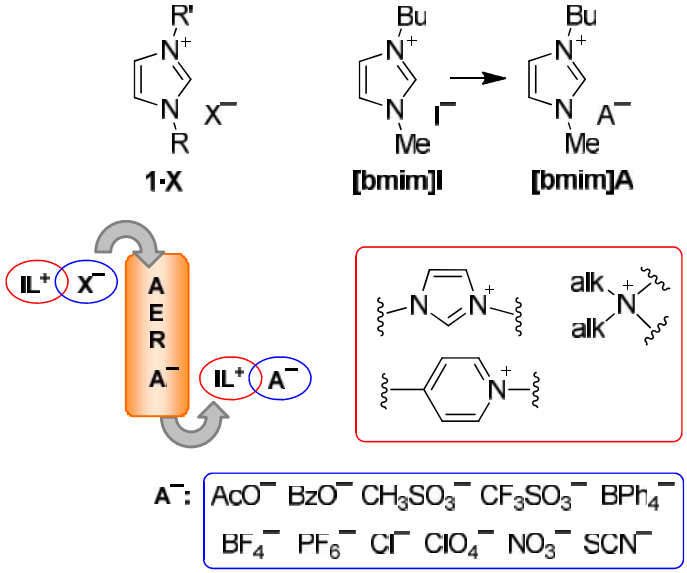
1. Introduction

Azolium systems have gained a place among the anion-binding functional groups, ranging from anion receptors and sensors to transporters [2-9], and as ionic liquids (ILs) their utility has expanded into domains beyond chemistry [10-14]. The greenness of the most established IL syntheses and purification procedures has been analyzed and evaluated [13]. Thus, the chemical aspects of imidazolium-based ILs, including their synthesis, counteranion exchange and purity, have been the subject of numerous studies with the aim of obtaining pure IL salts, especially halide-free ion pairs. However, little attention has been paid to the use of an anion exchange resin (AER) [1,12-14]. Examples of anion exchange resin application to ILs reported in the open literature use either the AER (OH^- form) or the AER (A^- form) method [1,14]. We have recently examined the preparation of an AER (A^- form) conveniently loaded with a selected anion after treatment with either acids or ammonium salts in water, or hydroalcoholic media, or organic solvents. The halide-to-anion exchange of quaternary imidazolium salts **1·X** and their transformation to the corresponding ion pairs **1·A** was carried out in methanol or organic solvents providing a pure ionic liquid in excellent to quantitative yields (Figure 1). Moreover, the transformation of both lipophylic quaternary heteroaromatic cations and low hydrophilic anions also proceeded in excellent to quantitative yields [1]. This simple procedure offers a convenient way to replace halide anions by a broad range of anions in and also eliminates halide impurities and minimizes the formation of toxic by-products with consequential environmental benefits.

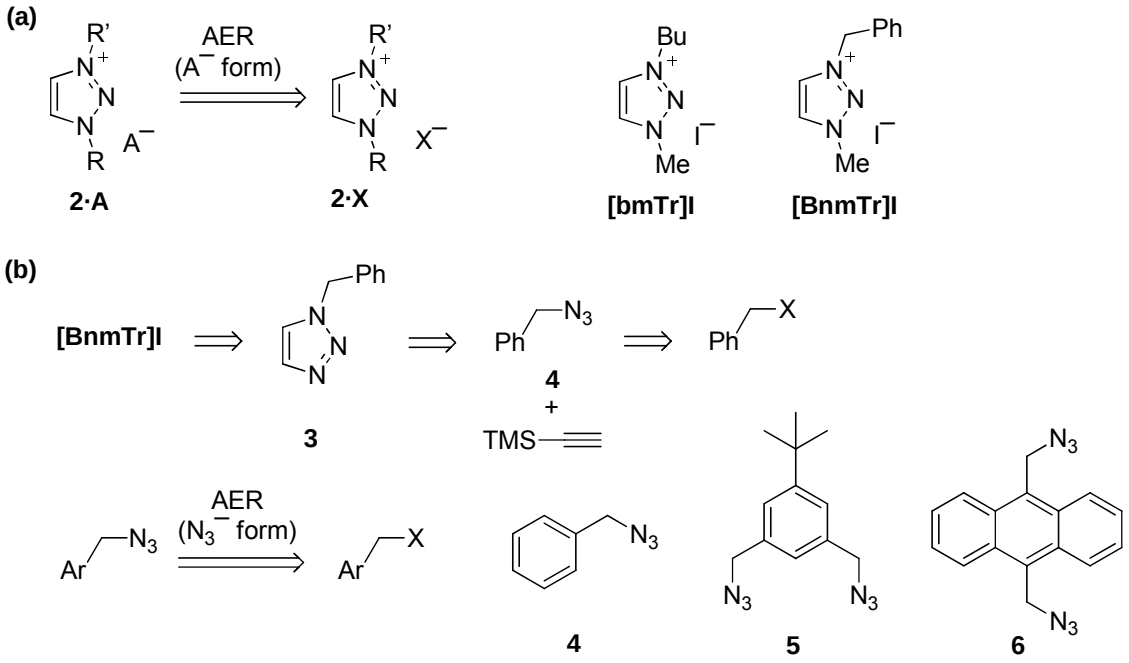
Figure 1. Application of the anion exchange resin (A^- form) method in non-aqueous media to representative imidazolium-based ionic liquids **1·X** [1].



A logical extension of our previous studies on imidazolium-based systems was to examine 1,3-dialkyl-1,2,3-triazolium **2·X**, which have been recently described as stable and recyclable solvents [15]. The present study is focused on the application of the AER (A^- form) method for the iodide-to-anion exchange of the selected triazolium ion pairs. The recently reported synthesis of **[BnmTr]I** requires benzyl azide **4** for the preparation of the click-derived 1,2,3-triazole **3** [15], as shown in the

retrosyntetic Scheme 1. Thus, an AER (N_3^- form) was prepared and used to obtain azide **4** and bis(azidomethyl)arenes **5** and **6**. It should be noted that in the last years theoretical calculations have confronted the question of what is responsible for the anion−cation non-covalent interactions in pure imidazolium-based ILs and have challenged the role of $(C-H)^+$ hydrogen bonds in explaining IL properties [16,17]. A relevant part of the present study is focused on the significance of the noncovalent interactions involved between the azolium motifs and a variety of anions, with special attention given to nonclassical charged-assisted $(C–H)^+\cdots$anion hydrogen bonds. Thus, the ion pairs prepared provided the opportunity to learn about the hydrogen-bonding interactions of simple azolium systems such as 1-butyl-3-methylimidazolium and 1-benzyl-1-methyl-1,2,3-triazolium salts in solution-phase by proton NMR spectroscopy.

Scheme 1. 1,2,3-Triazolium-based ionic liquids **2·X**. **(a)** Halide-to-anion exchange: the anion exchange resin (A^- form) method. **(b)** Retrosynthetic pathway to the ion pair **[BnmTr]I** and to benzylic azides **4**, **5** and **6**.



2. Results and Discussion

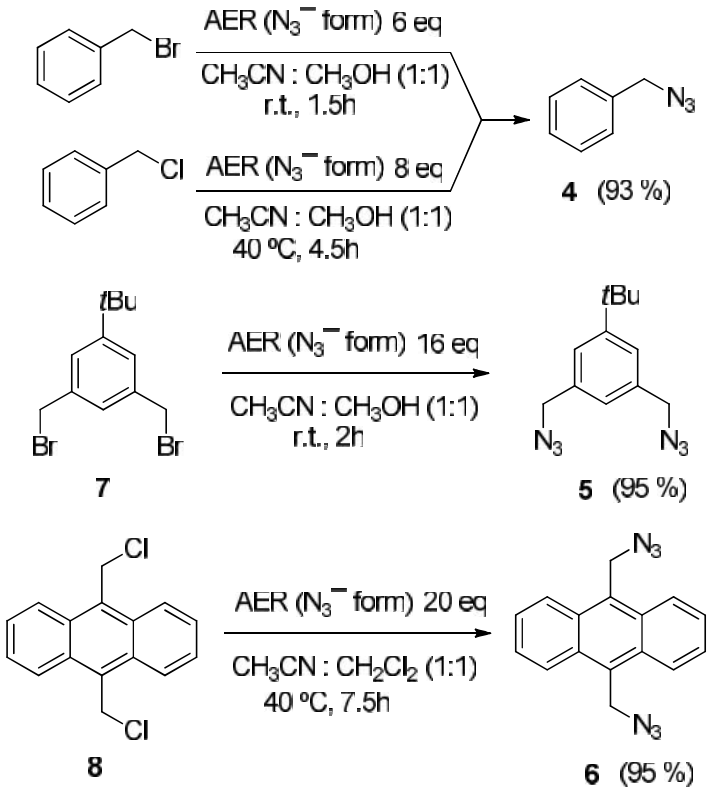
2.1. Preparation of benzylic azides using an anion exchange resin (N_3^- form)

Applications of ion-exchange resins to a variety of chemical reactions have proven to be extremely useful in different chemical fields such as organic synthesis, catalysis and industrial applications [18,19] as well as chemistry in flow systems [20]. The benzyl azide component **4** was prepared in excellent yield using a polymeric azide reagent protocol that consists of mixing benzyl bromide or chloride with 12 equivalents of the AER Amberlite IRA-400 (N_3^- form) at room temperature in dichloromethane [21], and also under standard reaction conditions between sodium azide and benzyl iodide or bromide at room temperature in a dipolar aprotic solvent, e.g. dimethyl sulfoxide or

dimethylformamide, in ≥ 91% yield [22,23], since benzylic halides readily undergo nucleophilic substitution reactions [24].

Following a modified experimental procedure previously reported by Hassner et al. [21], benzyl azide **4** was obtained in 93% yield from both benzyl bromide and chloride using a strong basic AER (N_3^- form) in CH_3CN/CH_3OH (1:1) (Scheme 2). Applying our protocol, bis(azidomethyl)arenes **5** and **6** were prepared by stirring the reaction mixture of the corresponding benzylic halides **7** and **8** and the azide-loaded strong basic AER (N_3^- form) in organic solvents under mild and safe conditions with a direct work-up. After examining various nucleophilic substitution reaction conditions, the best results were observed when using a solvent mixture of CH_3CN/CH_3OH (1:1) or CH_3CN/CH_2Cl_2 (1:1) to give the diazides **5** and **6**, respectively, in 95% yield (Scheme 2 and *subsection 3.8*).

Scheme 2. Preparation of benzyl azide **4** and bis(azidomethyl)arenes **5**, **6** using an azide-loaded strong basic AER (N_3^- form) in organic solvents.



2.2. Halide-to-anion exchange: AER (A^- form) method

The anion sources used to load the selected anions were mainly *via A* from acids or *via B* from the corresponding ammonium salt (Scheme 3 and Table 1). Thus, the AER (OH^- form) was packed in a column and treated with a hydromethanolic solution of the acid or ammonium salt. Following *via A*, the loading was performed with the hydromethanolic solution of AcOH or $MeSO_3H$ and the aqueous inorganic acids HPF_6 or HBF_4. In *via B*, anions such as $CF_3SO_3^-$, PF_6^- and BF_4^- were loaded in the resin using aqueous solutions of their ammonium salts, while the lipophilic BPh_4^- anion required CH_3CN/H_2O (9:1) solvent mixture. When the anions were loaded in the AER, we examined the efficiency of the counteranion exchange using 1,2,3-triazolium ionic liquids, due to their recent interest

as stable and recyclable solvents [15], e.g. **[bmTr]I** and **BnmTr]I**. A recent study has shown that the key physicochemical aspects of 1,2,3-triazolium-based ILs are their high electrochemical stability and ionic conductivity, which are comparable to their imidazolium counterparts, yet with the advantage that the 1,2,3-triazolium nucleus seems to be more robust under alkaline reaction conditions [25].

Scheme 3. AER (A^- form) method applied to 1,2,3-triazolium ionic liquids **[bmTr]I** and **[BnmTr]I**. **(a)** Anion loading and anion source. **(b)** Iodide-to-anion exchange of **[bmTr]I** and **[BnmTr]I**.

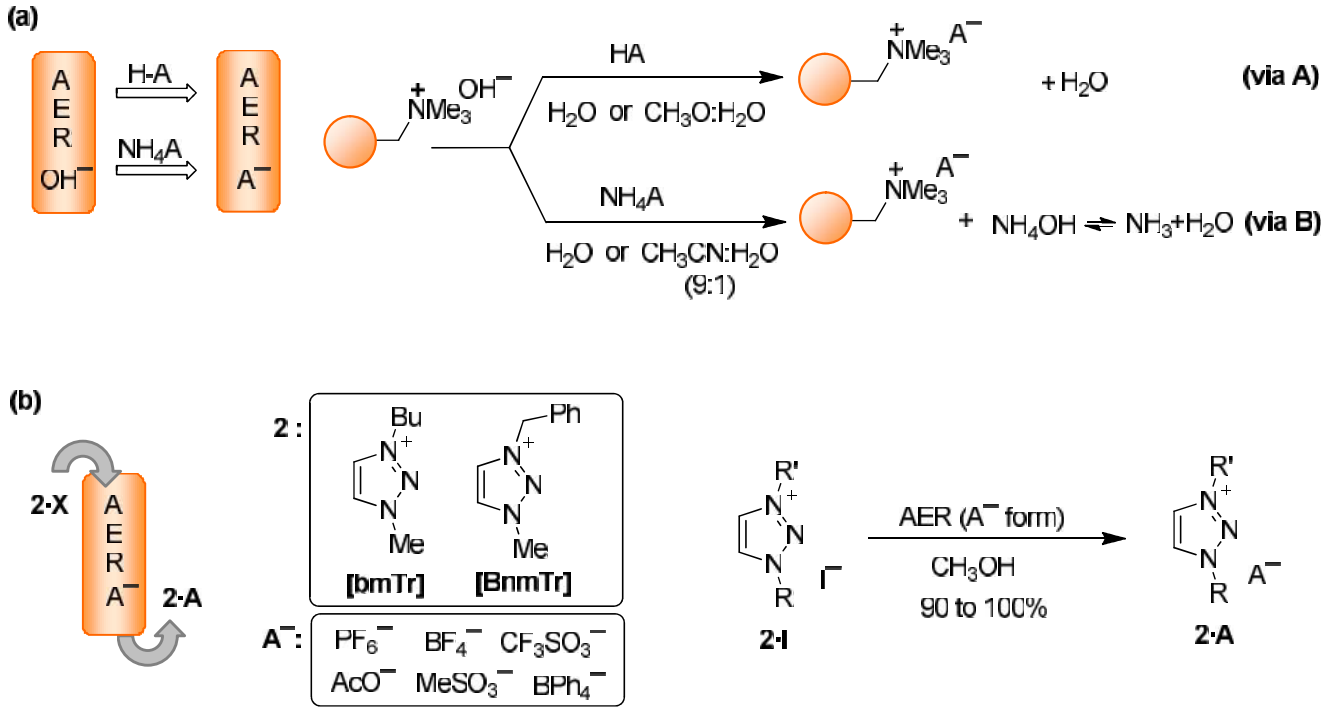


Table 1. Iodide-to-anion exchange of 1,2,3-triazolium-based ionic liquids **[bmTr]I** and **[BnmTr]I** in methanol.

Anion	Loading[a]	[bmTr]		[BnmTr]	
		Yield (%)[b]	I^- (ppm)[c]	Yield (%)[b]	I^- (ppm)[c]
AcO^-	via A[d]	100	<20	100	<20
$MeSO_3^-$	via A[d]	92	<20	94	<20
PF_6^-	via A[e] or via B[e]	90	20-40	97	<20
BF_4^-	via A[e] or via B[e]	94	20-40	90	20-40
$CF_3SO_3^-$	via B[d]	93	20-40	92	<20
BPh_4^-	via B[f]	92	<20	—	

[a]Anion source: via A and/or via B (Scheme 3). [b]Isolated yield. [c]Halide contents after anion exchange determined by the silver chromate test. [d]Solvent loading: $CH_3OH:H_2O$. [e]Solvent loading: H_2O. [f]Solvent loading: $CH_3CN:H_2O$ (9:1).

The AER (A^- form) method was then applied to both 1,2,3-triazolium compounds **[bmTr]I** and **[BnmTr]I**, and the halide exchange for representative anions proceeded in 90% to quantitative yields

when methanol was used (Table 1), improving the results obtained using classical methods [15]. However, when the recovery of the new ion pairs **[IL]A** was around 90%, further studies to increase the yield using a less polar solvent, for example acetonitrile, were not carried out.

The characterization of the prepared ion pairs was confirmed by spectroscopic and spectrometric methods, especially ^{1}H NMR, and when necessary unambiguous assignments were made by NOESY experiments at 400 MHz. Moreover, the amount of halide content was determined by a silver chromate test following a similar protocol to that described by Sheldon and co-workers [26]. Additionally, it should also be considered that the AER used in the exchange can be recycled by treatment with 10% NaOH aqueous solution, and the recovered AER (OH^- form) can be re-utilized for a new anion loading. The chosen strong AER was Amberlyst A-26 but other similar AERs, which allow the use of aqueous mixtures and non-aqueous solvents, can be used instead.

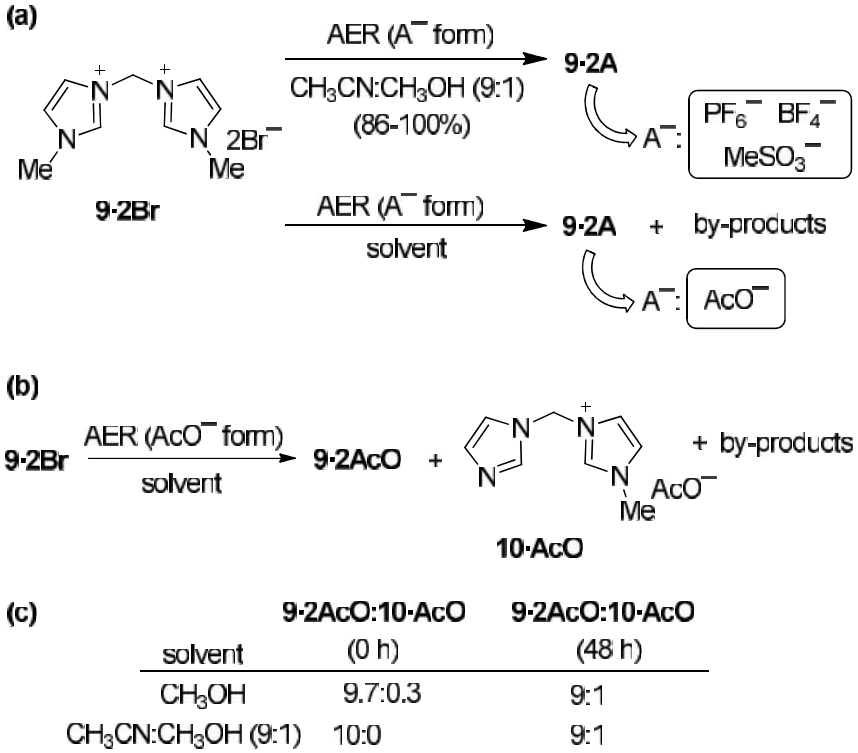
2.3. Scope and limitations of the anion exchange using the AER (A^- form) method

When applied to known imidazolium-based systems for anion recognition and ionic liquids, the counteranion exchange proceeded in excellent to quantitative yields and confirmed the versatility and benefits of the AER (A^- form) method in organic solvents with a range of polarity [1]. The most appropriate solvent or solvent mixture was then chosen according to the hydrophobic nature of both the cation and the counteranion species. A limiting factor of this counteranion exchange method, however, concerns the chemical stability of the cationic and oligocationic systems in basic media. The basicity of the counteranions [14,27-29] could modulate the chemical response of the resulting ion pairs, although this is not a restriction of the AER (A^- form) method itself.

A brief study was then centered on the versatility of the AER (A^- form) method when applied to a known building block such as the bis(imidazolium) salt with a methylene interannular spacer **9·2Br** [30,31], which provided a simple model to examine the chemical response under the conditions of the counteranion exchange protocol that makes use of a strong basic AER (A^- form) in organic solvents, Scheme 4.

A methanolic solution of the bis(imidazolium) salt **9·2Br** was passed through a column packed with an AER (PF_6^- form) to obtain pure **9·2PF$_6$** in just 59% yield, which changed, however, to the more hydrophobic solvent mixture CH_3CN:CH_3OH (9:1), the bromide-to-hexafluorophosphate exchange progressing in quantitative yield. The use of the corresponding AER (A^- form) in similar conditions gave pure **9·2BF$_4$** and **9·2MeSO$_3$** ion pairs in 96% and 86% yields, respectively (Scheme **4**). When the bromide ion was displaced by more basic anions such as acetate, the new bis(imidazolium) ion pair **9·2AcO** turned out to be rather unstable in solution and also in pure oil form. The chemical response of the **9·AcO** ion pair in solution was followed by ^{1}H NMR spectroscopy of aliquots over 2 days and the bis(imidazolium) acetate was partially transformed to the demethylated cationic counterpart **10·AcO**, along with by-products. Although initially the chemical instability of **10·AcO** seemed more evident in methanolic solution, after 48 h at room temperature in either CH_3OH or CH_3CN:CH_3OH (9:1) the relative proportions of the ion pairs **9·2AcO** and **10·AcO** was 9:1 (Scheme 4), and this was not studied further.

Scheme 4. Application of the AER (A^- form) method to bis(imidazolium) salts with a methylene interannular spacer **9·2Br**. **(a)** Transformation of **9·2Br** to **9·2A** in ≥ 86% yield using the solvent mixture CH_3CN:CH_3OH (9:1). **(b)** Chemical response of compound **9·2AcO** in methanol and acetonitrile. **(c)** The ratio of bis(imidazolium) salt **9·2AcO** and the cationic demethylated counterpart **10·AcO** in methanol and acetonitrile over 2 days.



(c)

solvent	9·2AcO:10·AcO (0 h)	9·2AcO:10·AcO (48 h)
CH_3OH	9.7:0.3	9:1
CH_3CN:CH_3OH (9:1)	10:0	9:1

2.4. ^1H NMR spectroscopy

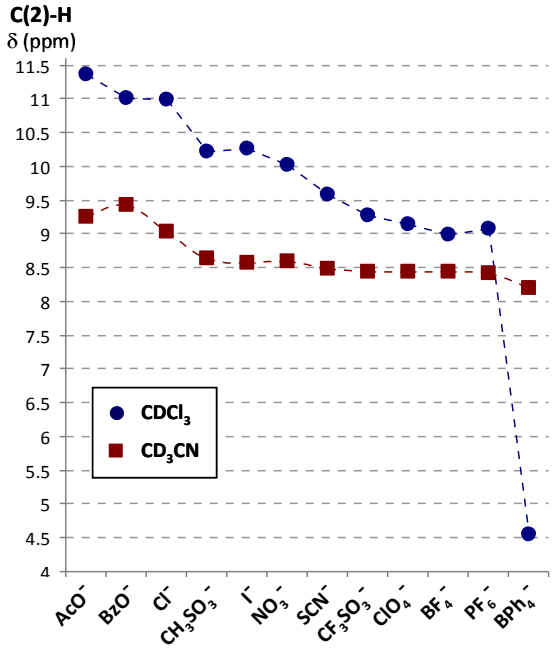
Imidazolium-based systems form a bridge between the chemistry of ionic liquids (ILs) and anion recognition, notable noncovalent driving forces being a combination of electrostatics and hydrogen bond interactions [6,32]. Particularly significant is the role of the non-classical $(C–H)^+\cdots$anion hydrogen bonds in imidazolium-based anion receptors, sensors and carriers, as well as in ILs, which has sparked a flurry of interest and debate in the last few years. Evidence for hydrogen bonding in the solid phase of the simple 1-ethyl-3-methylimidazolium salt **[emim]I** was first reported by Seddon and co-workers in 1986 [33] and then later for **[emim]Br** and **[emim][AlBr$_4$],** using single-crystal X-ray diffraction analysis [34,35], and confirmed in the solution-phase by multinuclear NMR spectroscopy [36]. Moreover, Ludwig and co-workers reported direct spectroscopic evidence for an enhanced cation-anion interaction driven by $(C–H)^+\cdots$anion hydrogenbonds in pure ILs, which strengthened the role of hydrogen bonds in imidazolium ILs [16,17].

Depending on the structure of the imidazolium-based frameworks, other noncovalent intermolecular interactions can also take place between cations and counteranions, a case in point being the usually weaker CH/π noncovalent interactions that can be rather significant for anions bearing aromatic units, e.g. tetraphenylborate [6]. Thus, the structural study of **[bmim][BPh$_4$]** reported by Dupont et al. revealed the presence of $(C–H)^+\cdots\pi$ hydrogen bonds both in solution phase and solid state [37,38]. The

anion effect has also been examined by Lungwitz and Spange using the representative **[bmim]A** ion pairs in dichloromethane as the solvent, which in fact should lower solvation of the ion pairing in favor of contact ion pairs. A hydrogen-bond accepting (HBA) ability scale was then established for varied anions of the **(bmim$^+$)** cation by means of ^{1}H NMR spectroscopy, at concentrations of 0.02 or 1.8 M, in CD_2Cl_2, and the HBA capacity of anions directly affected chemical shift values in the imidazolium moiety, especially the C(2)-H of the imidazolium ring [39]. As already mentioned, the use of CD_2Cl_2 as a solvent implies minimizing solute-solvent interactions [38,40].

The ^{1}H NMR data obtained from the routine checking of the quaternary heteroaromatic salts [**ILs]A** provide useful information about the noncovalent interactions between the cations and the counteranions. Moreover, it serves to verify the exchange process since, as expected, when the new anion was organic, the comparison of the relative integration of both charged moieties showed the degree of the halide swap. The ^{1}H NMR spectral data of **[bmim]A** in a 0.02 M concentration were registered in $CDCl_3$ and CD_3CN and the chemical shift values of C(2)-H of the imidazolium ring were compared, as shown in Figure 2. Standard reference values were obtained from samples whose purity had been confirmed by other techniques. This enabled a pattern of proton chemical shift values to be established, which was then used to check the halide-for-inorganic anion exchange. The proton chemical shift differences were more evident in $CDCl_3$ in the range of 2 ppm, with the exception of **[bmim][BPh$_4$]**, compared with the nonhydroxylic dipolar CD_3CN, which is only in the range of 1 ppm (see below).

Figure 2. 1-butyl-1-methylimidazolium salts **[bmim]A**: ^{1}H NMR C(2)-H chemical shift at 300MHz of a 0.02 M solution in $CDCl_3$ (●) and CD_3CN (■).



Qualitative ^{1}H NMR analysis. It is well established that the chemical shifts of the acidic C(2)–H protons in the imidazolium motifs are the most sensitive to the nature of the counteranion, solvent polarity and structural factors of imidazolium-based systems such as anion receptors and sensors [6] as well as ILs [38]. Accordingly, ionic liquids **[bmim]A** and **[BnmTr]A** were further examined by ^{1}H NMR in $CDCl_3$ and CD_3CN at concentrations of 0.002 and 0.02 M to ascertain the influence of the

counteranion and the solvent polarity on the proton chemical shifts of the C(2)-H of imidazolium and the C(4)-H and C(5)-H of 1,2,3-triazolium cations (Table 2).

The observed proton NMR chemical shifts of **[bmim][BPh$_4$]** at concentrations of either 0.002 M or 0.02 M showed a greater shielding in $CDCl_3$ for C(2)-H (δH = 4.83 ppm or δH = 4.54 ppm) while in a dipolar-aprotic solvent such as CD_3CN, this interaction was weakened by solvation (δH = 8.31 ppm or δH = 8.19 ppm). These results are in accordance with the abovementioned in-depth structural study of **[bmim][BPh$_4$]** reported by Dupont et al. [37].

The tendency of the imidazolium molecular motif in selected **[bmim]A** ion pairs to form non-classical hydrogen bonds $(C–H)^+\cdots$anion was then qualitatively examined by ^{1}H NMR and the greatest deshielding effect corresponded to the acidic C(2)-H of the imidazolium cation depending on: (a) the nature of the counteranion, *e.g.* AcO^-, Cl^- and the weakly-coordinating and charge diffuse PF_6^- anion, and (b) the solvent polarity, *e.g.* $CDCl_3$ and CD_3CN at different concentrations (Table 2). Likewise, the ^{1}H NMR of the quaternary 1,2,3-triazolium salts **[BnmTr]A** when the counteranions are AcO^-, or Cl^-, or PF_6^- in $CDCl_3$ and CD_3CN exhibited similar trends corresponding to the ring protons C(4)-H and C(5)-H, the results being summarized in Table 2.

Table 2. Selected ^{1}H NMR (300 MHz) chemical shift values of **[bmim]A** and **[BnmTr]A** in $CDCl_3$ and CD_3CN at concentrations of 0.02 M and 0.002 M.

[bmim]A	Solvent	0.002 M			0.02 M			[BnmTr]A	Solvent	0.002 M		0.02 M	
		H-2	H-4	H-5	H-2	H-4	H-5			H-4	H-5	H-4	H-5
AcO^-	$CDCl_3$	11.81	7.08	7.07	11.35	7.09	7.08	AcO^-	$CDCl_3$	9.91	9.60	9.60[b]	9.44[b]
	CD_3CN	8.93	7.34	7.31	9.25	7.35	7.32		CD_3CN	8.61	8.43	8.89	8.61
	Δδ[a]	+2.88	–0.26	–0.24	+2.10	–0.26	–0.24		Δδ[a]	+1.30	+1.17	+0.71	+0.83
Cl^-	$CDCl_3$	11.19	7.16	7.16	10.99	7.31	7.24	Cl^-	$CDCl_3$	9.37	9.24	9.41	9.33
	CD_3CN	8.70	7.36	7.33	9.04	7.39	7.36		CD_3CN	8.33	8.28	8.40	8.32
	Δδ[a]	+2.49	–0.20	–0.17	+1.95	–0.08	–0.12		Δδ[a]	+1.04	+0.96	+1.01	+1.01
PF_6^-	$CDCl_3$	8.97	7.23	7.21	9.07	7.26	7.23	PF_6^-	$CDCl_3$	8.71	8.59	8.84	8.74
	CD_3CN	8.38	7.34	7.31	8.42	7.35	7.31		CD_3CN	8.31	8.26	8.32	8.27
	Δδ[a]	+0.59	–0.11	–0.10	+0.65	–0.09	–0.08		Δδ[a]	+0.40	+0.33	+0.52	+0.47
BPh_4^-	$CDCl_3$	4.83	6.58	6.50	4.54	6.01	5.84						
	CD_3CN	8.31	7.32	7.26	8.19	7.27	7.27						
	Δδ[a]	–3.48	–0.74	–0.76	–3.65	–1.26	–1.43						

[a]Δδ, observed chemical shift difference between values obtained in $CDCl_3$ and CD_3CN.
[b]Unambiguous assignments were made by NOESY-1D (400 MHz).

3. Experimental Section

3.1. General

Ion exchanger resin Amberlyst A-26 (Aldrich, OH^- form), benzylbromide, benzylchloride and **[bmim]I** together with all acids, ammonium salts, reagents and solvents were purchased from commercial suppliers, unless mentioned otherwise, and used without further purification. All solvents were reagent grade and methanol and THF were distilled prior to use. **[bmTz]I** [15], **[BnmTz]I** [15],

1,3-bis(bromomethyl)-4-*tert*-butylbenzene **7** [41], 9,10-bis(chloromethyl)antracene **8** [42], and 1,1'-methylene-3,3'-dimethyldiimidazolium dibromide **9·2Br** [30] were prepared according with the literature. ^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) or Mercury 400 (400 MHz) spectrometers at 298 K. Chemical shifts were referenced and expressed in ppm (δ) relative to the central peak of DMSO-d_6 (2.49 ppm), CD3CN (1.94 ppm) and TMS for chloroform-*d*. ^{13}C NMR spectra were recorded on a Varian Gemini 300 (75.4 MHz) or Mercury 400 (100.6 MHz) spectrometer at 298 K. IR spectra were recorded on a Thermo Nicolet Avatar 320 FTIR apparatus. Mass spectrometric analyses were performed by using EI at 70 eV in a Hewlett-Packard spectrometer (HP-5989A model) or by using CI at 120 eV in a Thermo Finnigan TRACE DSQ spectrometer. ESI(+)-MS and ESI(-)-MS mass spectra were obtained on a LC/MSD-TOF (2006) mass spectrometer with a pumping system HPLC Agilent 1100 from Agilent Technologies at Serveis Científico-Tècnics of universitat de Barcelona. Melting points was measured in a Gallenkamp Melting Point Apparatus MPD350.BM2.5 with digital thermoter and are uncorrected. The pH was measured with benchmeter pH1100 (Eutech Instrunments), using Hamilton Flushtrode pH electrode for hydroalcoholic solutions.

The amount of halide contents was determined by a silver chromate test following a similar protocol to that described by Sheldon and co-workers [26]. An aqueous solution (5 mL) of potassium chromate (5 % p/v in Milli-Q water, 0.257 M) was added to the sample (5-10 mg). To 1 mL of the resulting dark yellow solution was added a minimum amount of silver nitrate aqueous solution (0.24 % p/v in Milli-Q water, 0.014 M). A persistent red suspension of silver chromate would be observed if the sample was free of halide. The minimum measurable amount of silver nitrate aqueous solution was 0.011 mL; consequently, the detection limit is approx. 6 ppm for Cl^-, 13 ppm for Br^- or 20 ppm for I^-. The halide content was determined at least twice for each sample.

Additionally, the use of alumina and silica columns can leave a low level of residual particulate contamination in ILs[1,14] and then, nano-particulates may also be an issue when using strongly basic anion exchange resins (A^- form). However, the analysis of possible particulate contamination was beyond the scope of the present study.

3.2. Preparation of the AER ($N3^-$ form)

3.5 g of wet Amberlyst® A-26 (OH^- form) were packed in a glass column and washed with H_2O (50 mL). A 10% NaN_3 aqueous solution (65 mL, 100 mmol) was passed slowly through the AER (OH^- form) until the pH of eluates was reached to the same value than the original solution. Then, AER (N_3^- form) was washed generously with H_2O, H_2O:CH_3OH progressive mixtures (9:1, 7:3, 5:5, 3:7, 1:9; 50 mL of each mixture) and CH_3OH:CH_3CN progressive mixtures (9:1, 7:3, 5:5; 50 mL of each mixture). The calculated amount of N_3^- loaded in the resin is 5.8 mmol/g [1].

*3.3. Benzylazide **4***

From benzylchloride. The AER (N_3^- form) (12 g , 69.4 mmol of N_3^-) was added to a solution of benzylchloride (1.099 g, 1 mL, 8.68 mmol) in 30 mL of CH_3CN: CH_3OH (1:1) solvent mixture, and the suspension was heated under stirring at 40 ºC for 2.5 h. The AER was filtered and the solvent was eliminated under vacuum providing the oily pure benzylazide **4** (1.069 g, 93% yield). As a caution the product was stored in the freezer until further use.

From benzylbromide. The AER (N_3^- form) (8.7 g , 50.3 mmol of N_3^-) was added to a solution of benzylbromide (1.438 g, 1 mL, 8.40 mmol) in 30 mL of CH_3CN: CH_3OH (1:1) solvent mixture, and the suspension was stirred at room temperature for 1.5 h. The AER was filtered and the solvent was eliminated under vacuum, providing the oily pure benzylazide **4** (1.040 g, 93% yield). As a caution, the product was stored in the freezer until further use. IR (NaCl): υ (N_3) 2096 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.35 (s, 2H), 7.36-7.40 (m, 5H).

*3.4. 1,3-bis(azidomethyl)-4-tert-butylbenzene **5***

The AER (N_3^- form) (3.45 g , 20 mmol of N_3^-) was added to a solution of 1,3-bis(bromomethyl)-4-*tert*-butylbenzene **7** (0.400 g, 1.250 mmol) in 25 mL of CH_3CN:CH_3OH (1:1) solvent mixture and the suspension was stirred at room temperature for 2 h. Then, the AER was filtered, washed with CH_3CN:CH_3OH (1:1) (25 mL) and the solvent was removed under vacuum, to afford the pure diazide **5** (0.290 g, 95%) as orange oil. As a caution, the product was stored in the freezer until further use. IR (NaCl): ν(N_3) 2090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9H), 4.37 (s, 4H), 7.10 (s, 1H), 7.30 (s, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 31.2, 34.8, 54.9, 125.0, 125.1, 135.8, 152.7. CIMS *m/z* (%): 263 (75) [M+NH_4], 217 (100) [M+H − N_2]; 189 (74) [M+H − 2N_2].

*3.5. 9,10-bis(azidomethyl)antracene **6***

The AER (N_3^- form) (3.14 g , 18.18 mmol of N_3^-) was added to a solution of 9,10-bis(chloromethyl)antracene **8** (0.250 g, 0.909 mmol) in 40 mL of CH_3CN:CH_2Cl_2 (1:1) solvent mixture and the suspension was heated under stirring at 40 ºC for 7.5 h. The AER was filtered, washed with CH_3CN: CH_2Cl_2 (1:1) (25 mL) and the solvent was removed under vacuum, to afford the pure diazide **6** (0.290 g, 95%) as orange solid. As a caution, the product was stored in the freezer until further use. mp 107–108 °C. IR (KBr): ν(N_3) 2075 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.36 (s, 4H), 7.65 (m, 4H), 8.37 (m, 8H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 46.4, 124.5, 126.6, 128.1, 130.4.

3.6. Anion loading in the AER (OH^- form)

3.6.1. Acids as anion source (via A)

2.5 g (~ 3 cm^3) of commercial wet strongly basic anion exchange Amberlyst A-26 (OH^- form) was packed in a glass column (1 cm diameter) and washed with water, and the column bed was equilibrated progressively with water-methanol mixtures until reaching the selected solvent media used afterwards for anion loading (~ 25 mL of each solvent mixture). A 1% acid solution in the appropriate solvent was passed slowly through the resin until the eluates had the same pH value as the original selected acid solution, and then the resin was washed generously with solvent until constant pH. The process was carried out at room temperature, using gravity as the driving force.

3.6.2. Ammonium salts as anion source (via B)

2.5 g (~ 3 cm^3) of commercial wet strongly basic anion exchange Amberlyst A-26 (OH^- form) was packed in a glass column (1 cm diameter) and washed with water (~ 25 mL). A 1% ammonium salt aqueous solution was passed slowly through the resin until the eluates had the same pH value as the original selected acid solution, and then the resin was washed generously with water until constant pH. The process was carried out at room temperature, using gravity as the driving force. In order to load BPh_4^- anion, a CH_3CN:H_2O (9:1) solvent mixture was used and the process involves to wash the AER (OH^- form) with the same solvent mixture previously to pass the ammonium salt solution.

3.7. Anion exchange: general procedure

A solution of the triazolium salt (0.5-0.6 mmol) in 10 mL of methanol was passed slowly through a column packed with ~ 3 cm^3 of AER (A^- form), and then washed with 25 mL of solvent. The combined eluates were evaporated, and the residue obtained was dried in a vacuum oven at 60 ºC with P_2O_5 and KOH pellets.

[bmTz][AcO]. Iodide exchange of **[bmTz]I** was carried out with AER (AcO^- form) following the general procedure described above, and using CH_3OH as solvent. Brown oil (quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H), 1.38 (m, 2H), 1.94 (s, 3H, AcO), 1,98 (m, 2H), 4.42 (s, 3H), 4.64 (t, 2H), 9.66 (s, 1H), 9.92 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[bmTz][MeSO$_3$]. Iodide exchange of **[bmTz]I** was carried out with AER ($MeSO_3^-$ form) following the general procedure described above, and using CH_3OH as solvent. Yelow oil (92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H), 1.40 (m, 2H), 1,99 (m, 2H), 2.76 (s, 3H, $MeSO_3$), 4.45 (s, 3H), 4.68 (t, 2H), 9.22 (s, 1H), 9.32 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[bmTz][BPh$_4$]. Iodide exchange of **[bmTz]I** was carried out with AER (BPh_4^- form) following the general procedure described above, and using CH_3OH as solvent. Light brown solid (92% yield). mp 149-50 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, 3H), 1.13 (m, 2H), 1,50 (m, 2H), 3.00 (s, 3H), 3.49 (t, 2H), 5.48 (s, 1H), 5.50 (s, 1H), 6.78 (d, 8H), 6.95 (t, 4H), 7.51 (t, 8H). Iodide content < 20 ppm according silver chromate test.

[bmTz][PF$_6$]. Iodide exchange of **[bmTz]I** was carried out with AER (PF_6^- form) following the general procedure described above, and using CH_3OH as solvent. Yelow oil (90% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, 3H), 1.40 (m, 2H), 2.00 (m, 2H), 4.38 (s, 3H), 4.60 (t, 2H), 8.59 (s, 1H), 8.63 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[bmTz][CF$_3$SO$_3$]. Iodide exchange of **[bmTz]I** was carried out with AER ($CF_3SO_3^-$ form) following the general procedure described above, and using CH_3OH as solvent. Yelow oil (93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H), 1.37 (m, 2H), 1.96 (m, 2H), 4.36 (s, 3H), 4.59 (t, 2H), 8.74 (s, 1H), 8.76 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[bmTz][BF$_4$]. Iodide exchange of **[bmTz]I** was carried out with AER (BF_4^- form) following the general procedure described above, and using CH_3OH as solvent. Yelow oil (94% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, 3H), 1.40 (m, 2H), 2.00 (m, 2H), 4.39 (s, 3H), 4.14 (t, 2H), 8.66 (s, 1H), 8.73 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[BnmTz][AcO]. Iodide exchange of **[BnmTz]I** was carried out with AER (AcO^- form) following the general procedure described above, and using CH_3OH as solvent. Colorless oil (quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H, AcO), 4.40 (s, 3H), 5.82 (s, 2H), 7.42 (m, 3H), 7.47 (m, 2H), 9.44 (s, 1H), 9.60 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[BnmTz][MeSO$_3$]. Iodide exchange of **[BnmTz]I** was carried out with AER ($MeSO_3^-$ form) following the general procedure described above, and using CH_3OH as solvent. Colorless oil (94% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78 (s, 3H, $MeSO_3$), 4.43 (s, 3H), 5.87 (s, 2H), 7.40 (m, 3H), 7.52 (m, 2H), 9.25 (s, 1H), 9.29 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[BnmTz][PF$_6$]. Iodide exchange of **[BnmTz]I** was carried out with AER (PF_6^- form) following the general procedure described above, and using CH_3OH as solvent. Yelow oil (97% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.37 (s, 3H), 5.75 (s, 2H), 7.44 (m, 5H), 8.74 (s, 1H), 8.84 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[BnmTz][CF$_3$SO$_3$]. Iodide exchange of **[BnmTz]I** was carried out with AER ($CF_3SO_3^-$ form) following the general procedure described above, and using CH_3OH as solvent. Colorless oil (92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.37 (s, 3H), 5.75 (s, 2H), 7.43 (m, 3H), 7.48 (m, 2H), 8.71 (s, 1H), 8.78 (s, 1H). Iodide content < 20 ppm according silver chromate test.

[BnmTz][BF$_4$]. Iodide exchange of **[BnmTz]I** was carried out with AER (BF_4^- form) following the general procedure described above, and using CH_3OH as solvent. Yelow oil (90% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 (s, 3H), 5.72 (s, 2H), 7.40 (m, 3H), 7.46 (m, 2H), 8.51 (s, 1H), 8.55 (s, 1H). Iodide content < 20 ppm according silver chromate test.

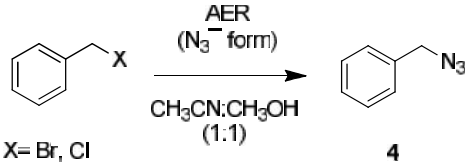
1,1'-methylene-3,3'-dimethyldiimidazolium dihexafluorophosphate (**9·2PF$_6$**). Bromide exchange of **9·2Br** was carried out with AER (PF_6^- form) following the general procedure described above, and using CH_3CN:CH_3OH (9:1) solvent mixture. White solid (quantitative yield). mp 168-9 ºC. ^{1}H NMR (300 MHz, CD_3CN): δ 3.88 (s, 6H), 6.38 (s, 2H), 7.44 (s, 2H), 7.57 (s, 2H), 8.73 (s, 2H). Bromide content < 13 ppm according silver chromate test.

1,1'-methylene-3,3'-dimethyldiimidazolium ditetrafluoroborate (**9·2BF$_4$**). Bromide exchange of **9·2Br** was carried out with AER (BF_4^- form) following the general procedure described above, and using CH_3CN:CH_3OH (9:1) solvent mixture. Light brown solid (96% yield). mp 150-1 ºC. ^{1}H NMR (300 MHz, CD_3CN): δ 3.88 (s, 6H), 6.42 (s, 2H), 7.44 (s, 2H), 7.63 (s, 2H), 8.84 (s, 2H). Bromide content < 13 ppm according silver chromate test.

1,1'-methylene-3,3'-dimethyldiimidazolium dimethansulphonate (**9·2MeSO$_3$**). Bromide exchange of **9·2Br** was carried out with AER ($MeSO_3^-$ form) following the general procedure described above, and using CH_3CN:CH_3OH (9:1) solvent mixture. White solid (86% yield). mp 194-6 ºC. ^{1}H NMR (300 MHz, CD_3CN): δ 2.56 (s, 6H, $MeSO_3^-$), 3.88 (s, 6H), 6.78 (s, 2H), 7.43 (s, 2H), 8.10 (s, 2H), 9.76 (s, 2H). Bromide content < 13 ppm according silver chromate test.

*3.8. Attempts to preparation of benzylazide **4** (Table 3), 1,3-bis(azidomethyl)-4-tert-butylbenzene **5** (Table 4) and 9,10-bis(azidomethyl)antracene **6** (Table 5)*

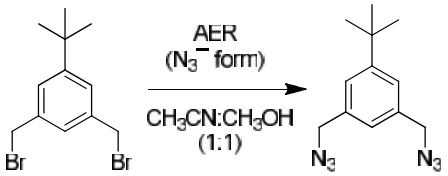
Table 3. Attempts to preparation of benzylazide **4** with AER (N_3^- form).



X	BnX mmol	N_3^- mmol[a]	Conc (M)[b]	T (ºC)	Time (h)	BnX : 4[c]	Yield (%)[d]
Br	8.4	26.1	1.68	r.t.	0.5	4.5 : 5.5	—
Br	8.4	26.1	0.42	r.t.	17	3.2 : 6.8	—
Br	8.4	34.8	1.68	r.t.	0.75	2.9 : 7.1	—
Br	8.4	34.8	0.28	r.t.	1.5	1.1 : 8.9	—
Br	8.4	50.46	0.28	r.t.	1.5	0 : 10	93
Cl	8.68	52.2	0.29	r.t.	1.5	7.4 : 2.6	—
Cl	8.68	52.2	0.29	40	4.5	1.6 : 8.4	—
Cl	8.68	60.9	0.29	40	3.5	0.5 : 9.5	—
Cl	8.68	69.4	0.29	40	4.5	0 : 10	93

[a]5.8 mmol/gr of AER (N_3^- form) [1]. [b]In MeCN:MeOH(1:1). [c]Calculated by ^{1}H NMR. [d]Isolated yield of compound **4**.

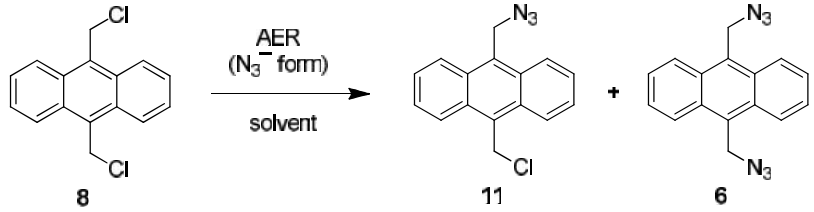
Table 4. Attempts to preparation of 1,3-bis(azidomethyl)-4-tert-butylbenzene **5** with AER (N_3^- form).



7 mmol	N_3^- mmol[a]	Conc (M)[b]	T (ºC)	Time (h)	7 : 5[c]	Yield (%)[d]
1.25	15.08	0.083	r.t.	1.5	1.5 : 8.5	—
1.25	15.08	0.05	r.t.	3.5	0.4 : 9.6	—
1.25	18	0.05	r.t.	3.25	0 : 10	95
1.25	20.3	0.05	r.t.	2	0 : 10	95

[a]5.8 mmol/gr of AER (N_3^- form) [1]. [b]In MeCN:MeOH (1:1). [c]Calculated by ^{1}H NMR. [d]Isolated yield of compound **5**.

Table 5. Attempts to preparation of 9,10-bis(azidomethyl)antracene **6** with AER (N_3^- form).

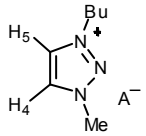


8 mmol	N_3^- mmol[a]	Conc (M)	solvent	T (ºC)	Time (h)	8 : 11: 6[b]	Yield (%)[c]
0.909	14.5	0.04	d	40	4	0 : 1.9 : 8.1	—
0.909	16.82	0.023	d	40	4	0 : 0.9 : 9.1	—
0.909	18.6	0.03	e	40	4	0 : 1 : 9	—
0.909	18.6	0.03	e	40	7.5	0 : 1.5 : 8.5	—
0.909	18.6	0.02	f	40	7.5	0 : 0 : 10	95

[a]5.8 mmol/gr of AER (N_3^- form) [1]. [b]Calculated by ^{1}H NMR. [c]Isolated yield of compound **6**. [d]CH_3CN: CH_3OH:CH_2Cl_2 (1:1:0.5). [e]CH_3OH:CH_2Cl_2 (1:1). [f]CH_3CN:CH_2Cl_2 (1:1).

*3.9. ^{1}H-NMR Data of Compounds **[bmTr]A** (Table 6) and **[BnmTr]A** (Table 7)*

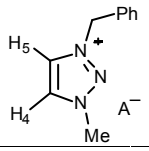
Table 6. ^{1}H NMR chemical shift values of 1-butyl-3-methyl-1,2,3-triazolium salt **[bmTr]A** in $CDCl_3$ and CD_3CN (300 MHz) at 298 K.[a]



Anion	Solvent	H-4	H-5	Me	Bu	A^-
AcO^-	$CDCl_3$	9.92	9.66	4.42	4.64; 1.98; 1.38; 0.96	1.94
$MeSO_3^-$	$CDCl_3$	9.32	9.22	4.45	4.68; 1.99; 1.40; 0.97	2.76
I^-[b]	$CDCl_3$	9.41	9.35	4.52	4.75; 2.03; 1.41; 0.97	
PF_6^-	$CDCl_3$	8.63	8.59	4.38	4.60; 2.00; 1.40; 0.98	
BF_4^-	$CDCl_3$	8.73	8.66	4.39	4.61; 2.00; 1.40; 0.98	
$CF_3SO_3^-$	$CDCl_3$	8.76	8.74	4.36	4.59; 1.96; 1.37; 0.94	
BPh_4^-	$CDCl_3$	5.50	5.48	3.00	3.49; 1.50; 1.13; 0.89	7.51; 6.95; 6.78
AcO^-	CD_3CN	8.67	8.67	4.26	4.57; 1.94; 1.36; 0.95	1.69
$MeSO_3^-$	CD_3CN	8.44	8.42	4.25	4.56; 1.94; 1.36; 0.95	2.42
I^-	CD_3CN	8.37	8.34	4.24	4.55; 1.95; 1.37; 0.95	
PF_6^-	CD_3CN	8.29	8.27	4.23	4.54; 1.93; 1.37; 0.95	
BF_4^-	CD_3CN	8.30	8.28	4.23	4.54; 1.93; 1.36; 0.95	
$CF_3SO_3^-$	CD_3CN	8.32	8.30	4.23	4.54; 1.94; 1.36; 0.95	
BPh_4^-	CD_3CN	8.19	8.16	4.18	4.45; 1.93; 1.35; 0.95	7.28; 7.00; 6.84

[a] Solution concentrations are 0.02 M. [b] Unambiguous assignments were made by NOESY-2D (400 MHz)

Table 7. ^{1}H NMR chemical shift values of 1-benzyl-3-methyl-1,2,3-triazolium salt **[BnmTr]A** in $CDCl_3$ and CD_3CN (300 MHz) at 298 K.[a]



Anion	Solvent	H-4	H-5	Me	CH_2-Ph	A^-
AcO^-[b]	$CDCl_3$	9.60	9.44	4.40	5.82; 7.47; 7.42	1.98
$MeSO_3^-$	$CDCl_3$	9.29	9.25	4.43	5.87; 7.52; 7.40	2.78
I^-	$CDCl_3$	9.41	9.33	4.51	5.97; 7.58; 7.44	
PF_6^-	$CDCl_3$	8.84	8.74	4.37	5.75; 7.44	
BF_4^-	$CDCl_3$	8.55	8.51	4.33	5.72; 7.46; 7.40	
$CF_3SO_3^-$	$CDCl_3$	8.78	8.71	4.37	5.75; 7.48; 7.43	
AcO^-	CD_3CN	8.89	8.61	4.24	5.80; 7.44	1.67
$MeSO_3^-$	CD_3CN	8.51	8.41	4.24	5.76; 7.46	2.42
I^-	CD_3CN	8.40	8.32	4.23	5.74; 7.45	
PF_6^-	CD_3CN	8.32	8.27	4.22	5.71; 7.45	
BF_4^-	CD_3CN	8.33	8.29	4.23	5.72; 7.46	
$CF_3SO_3^-$	CD_3CN	8.35	8.30	4.23	5.72; 7.46	

[a] Solution concentrations are 0.02 M. [b] Unambiguous assignments were made by NOESY-1D (400 MHz).

4. Conclusions

Against a pool of quaternary heteroaromatic ionic liquids, the azolium salts **[bmTr]I** and **[BnmTr]I** were chosen to validate the utility of the AER (A^- form) method in non-aqueous media for a halide exchanged by assorted anions. It was then confirmed that this simple method is efficient with 1,2,3-triazolium-based ionic liquids **2·X**, improving the currently operative procedures of classical counteranion exchange, *e.g.* **[bmTr][BF_4]**, **[bmTr][PF_6]** and **[bmTr][CF_3SO_3]** prepared from **[bmTr]I**. Recapping the results, the anion loading of the AER (OH^- form) with acids, ammonium salts and sodium azide was carried out in water or a hydromethanolic or CH_3CN/H_2O (9:1) solvent mixture according to the lipophilic nature of the anion source. Then, the anion exchange using the AER (A^- form) method in organic solvents was easily applied to the1,2,3-triazolium salts and the halide-to-anion exchange progressed in excellent to quantitative yields.

On the whole, the AER (A^- form) method in organic solvents is a method of choice for exchanging halide anions for a variety of anions in quaternary heteroaromatic salts, simultaneously removing halide impurities, which is often a troublesome task, and minimizing the formation of toxic by-products. In addition, the preparation of a few benzylic azides and diazides was carried out using an AER (N_3^- form) in organic solvent mixtures such as CH_3CN/CH_3OH (1:1) and CH_3CN/CH_2Cl_2 (1:1), resulting in a clean and mild protocol with easy work-up. The results of the ^{1}H NMR spectroscopic analysis focus attention on the significance of the charged-assisted $(C–H)^+\cdots$anion hydrogen bonds. Thus, a qualitative ^{1}H NMR comparison between 1-butyl-3-methylimidazolium salts and 1-benzyl-3-methyl-1,2,3-triazolium salts has shown that the nature of the azolium motifs modulated their ^{1}H NMR response.

Acknowledgments

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[†]Imidazolium-based frameworks. 25. Part 24: ref 1.

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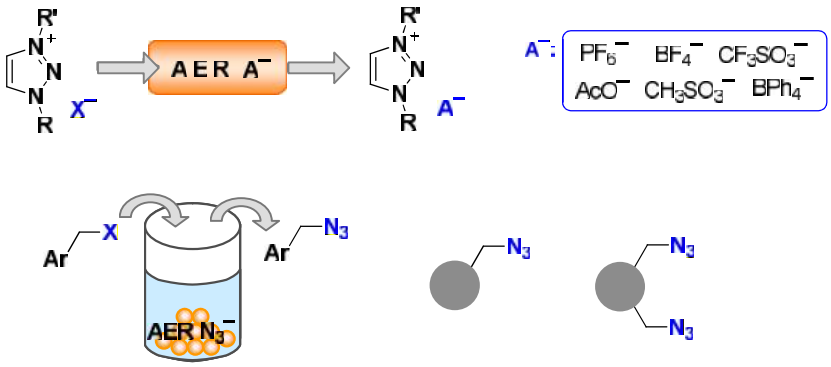
Sample Availability: Samples of all compounds are available from the authors.

Table of Contents Graphic



6. 2. PÒSTERS (CAPÍTOLS 3.2 i 4)

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in TNF-α and IL-6 secretion is observed in response to CPS and ATP. CPS induced NLRP3 inflammasome and IL-1β precursor (proIL-1β) expression through reactive oxygen species (ROS)-, ERK1/2-, and p38-associated pathways. Mitochondrial ROS and mitochondrial membrane permeability transition were found to be important for NLRP3 inflammasome activation in response to both CPS and ATP. The anti-CPS monoclonal antibodies protected mice from magA$^+$ *K. pneumoniae*-induced liver abscess formation and lethality. This indicates that the K1 epitope is a promising target for vaccine development.

Serological analysis of *K. pneumoniae* clinical isolates demonstrated that the O1 serotype was more prevalent in PLA strains than that in non-tissue-invasive strains (38/42 vs 9/32, p<0.0001). O1 serotype isolates had a higher frequency of serum resistance, and mutation of the O1 antigen changed serum resistance in *K. pneumoniae*. Our findings indicate that O1 antigen contributes to virulence by conveying resistance to serum killing, promoting bacterial dissemination to and colonization of internal organs after the onset of bacteremia, and could be a useful vaccine candidate against infection by PLA *K. pneumoniae*.

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P495

Imidazolium Arylacetates: Ionic Liquids for Drug Release

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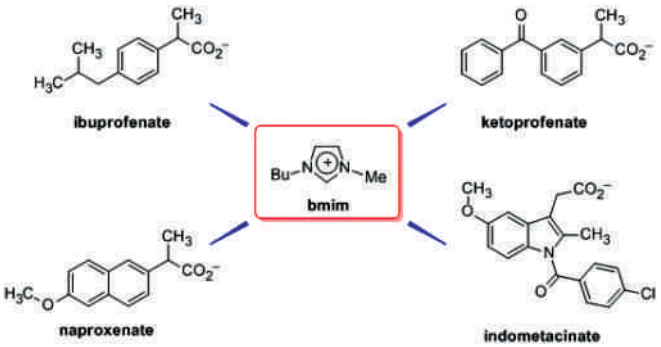
Besides their recognized value as an alternative to conventional solvents, ionic liquids (ILs) are becoming increasingly useful in a widening the range of fields in chemistry leaning toward biology. ILs make a unique architectural platform on which the properties of both cation and anion can be independently modified, providing tunability in the design of new functional materials as well as pharmaceutical and biological ingredients. In this way, their use enables to modulate the properties of active pharmaceutical ingredients (APIs) with novel performance enhancement and delivery options.

As a part of our ongoing research, we recently reported the anion exchange procedure in non-aqueous media as a simple method of choice to swap the halide ion of ILs for a broad range of anions, including ibuprofenate.[1] In order to extend our protocol to anti-inflamatory arylacetic acids, we herein report the preparation of several [bmim][R-CO_2] following AER (A^- form) method from selected examples of nonsteroidal anti-inflamatory drugs (NSAIDs). In addition, the study of the release from hyaluronan-based hydrogels as drug delivery system was carried out, considering that the high biocompatibility of this natural polysaccharide provides a good candidate for biomedical and pharmaceutical use.



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Synthesis and Biological Evaluation of Benzoxazines and Quinazoline-3-oxides

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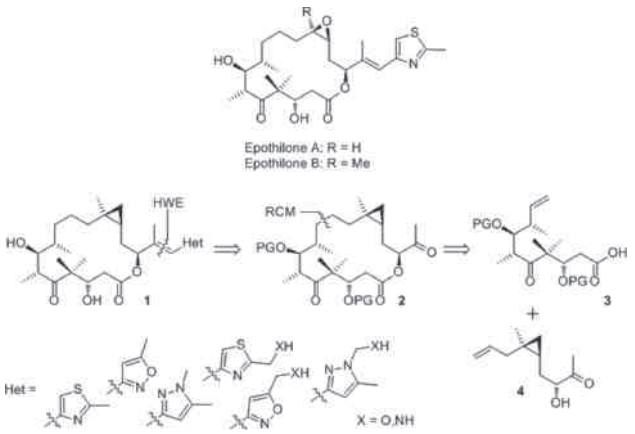
Benzoxazines and their analogues are a significant class of heterocycles involved in various biological properties such as inhibitory activity towards human leukocyte elastase and Clr serine protease enzymes. Numerous benzoxazine analogues were evolved as DNA binding antitumor agents and also act as progesterone receptor modulators. Several polymeric benzoxazines were explored as heat resistant and electronic materials. 4-Arylidene-2-aryl-4*H*-benzo[*d*]-[1,3]oxazines are synthesized with high stereoselectivity and regioselectivities from 2-alkynylbenzamides in the presence of catalytic amount of I_2. In the reaction mechanism, iodine plays a key role in two different aspects as a catalyst, such as to activate the alkyne with the iodinium donor which triggers the cascade, and then as a proper acid source to barrage catalyst recovery. The benzoxazines have been exploited as potential substrates for the synthesis of quinazoline-3-oxide derivatives directly in one step. Some compounds were found to show photodynamic therapy (PDT) applications against the melanoma as well oral cancer cell lines.



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P310

Heterophane Prototypes as Sensors and Transporters

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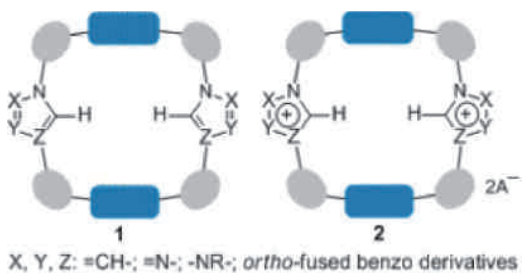
The demand for anionic synthetic receptors has been increasing rapidly in the fields of transport and extraction of anions and sensing mechanisms due to the number of fundamental roles played by anions in biological and chemical processes. In the last few years, azolium and azole functionalities have gained a place among the anion binding functional groups and have emerged as attractive starting points for the design of abiotic anion receptors.[1–4] This circumstance has given a biological perspective in the rapidly growing area of bionanotechnology, the aim of which is to develop new tools for biology, new biomaterials, selective sensors and supramolecular devices for clinical analysis, new therapeutics, and smart drug delivery systems. Continuing our research into azolium-based frameworks, herein we report the binding properties of heterophanes **1** and **2** with azole or azolium subunits as anion recognition motifs.



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P311

Multi-target Tri- and Tetracyclic Pseudoirreversible Butyrylcholinesterase Inhibitors Releasing Reversible Inhibitors with Neuroprotective Properties upon Carbamate Transfer

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Tri- and tetracyclic nitrogen-bridgehead compounds were designed and synthesized to yield micromolar cholinesterase (ChE) inhibitors as starting points for structure–activity relationships (SARs) that identified potent compounds with butyrylcholinesterase (BChE) selectivity. In a subsequent step, these structures were used for the design and synthesis of carbamate-based (pseudo)irreversible inhibitors. Compounds with further improved inhibitory activity and selectivity were obtained and kinetically characterized, also with regard to the velocity of enzyme carbamoylation. Structural elements were identified and introduced that showed additional neuroprotective properties on a hippocampal neuronal cell line (HT-22) after glutamate-induced generation of intracellular reactive oxygen species (ROS). We identified nanomolar and completely selective pseudoirreversible BChE inhibitors that release reversible inhibitors with neuroprotective properties after carbamate transfer to the active site of BChE.