



Ionic liquids in green analytical chemistry—are they that good and green enough?

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Abstract

The widespread use of ionic liquids (ILs) as greener solvents in analytical sciences, especially in sample pretreatment, has focused attention on exploiting their enormous potential, not only on eliminating and improving the drawbacks faced by scientists. These ionic compounds with unique physicochemical properties can be tuned through smart synthesis, combining cations and anions, so that the compound exhibits excellent properties for its intended purpose. Ionic liquids are rightly referred to as designer solvents. Validation of a newly proposed analytical methods using ionic liquids, either in sample preparation or in further analysis, is a critical process to demonstrate that a particular analytical method is fit for purpose and provides reliable and accurate results. In addition, this article specially addressed the potential toxicity of ionic liquids with the modest goal of assisting researchers in this field by expanding their target areas.

Keywords Green analytical chemistry (GAC) · Greener solvents · Green extractions · Toxicity of ionic liquids

Introduction

In recent decades, a large number of articles have been published reporting the extensive use of ionic liquids, as environmentally friendly solvents, mainly in (i) sample preparation of different matrixes, via solid-phase (micro) extraction (SPME), liquid-phase (micro)extraction (LPME), (ii) chromatographic and electrophoretic separations (gas chromatography, high-performance liquid chromatography, counter-current chromatography, capillary electrophoresis), (iii) mass spectrometry (ILs as matrixes in matrix-assisted laser desorption ionization, ILs as additives in electrospray ionization mass spectrometry), and (iv) electrochemical

sensing systems (ILs as electrolyte media, ionic liquid/carbon-based composite electrochemical sensing systems, ionic liquid/metal-based electrochemical sensing systems, biosensors based on ionic liquids) [1–3].

Various topics and objectives have been described and discussed in this still growing field with enormous potential based on the exquisite advantages of ILs as more environmentally friendly solvents. This group of ionic compounds is distinct from molten salts with a melting point below 100 °C or even at room temperature (RTILs—room temperature ionic liquids). Their unique physicochemical properties can be tuned by smart synthesis combining cations (e.g., imidazolium, benzimidazolium, pyrrolidinium, pyridinium, piperidinium, ammonium, phosphonium, guanidinium, or choline) and anions (e.g., alkyl sulfonate, tetrafluoroborate, hexafluorophosphate, chloride, bromide) to obtain the compound with excellent properties for the particular purpose. Ionic liquids are rightly called designer solvents [1, 2]. Paramagnetic anions, such as tetrachloroferrate(III), tetrachloromanganate(II), and tris(hexafluoroacetyl-aceto) manganate(II), are also desirable in the synthesis for the intended use of IL [1]. Negligibly low vapor pressure, high thermal stability, and high conductivity make them additionally attractive [4, 5]. The scope for analytical applications in the analysis of numerous analytes in different matrices is large. Some attractive examples will be briefly presented.

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It is not only fashionable but obligatory to follow the principles of green and white analytical chemistry (GAC and WAC) [6, 7]; it is a challenge to reduce the cost and environmental impact of ILs. Both of these aspects are lower for researchers working in academic settings than for those in industry because smaller amounts of ILs are typically used and less waste is generated after experiments. On the other hand, it is a great responsibility, a mission (why not?) for researchers in academia to address the problems of wasting ILs in the environment and to provide industry with strategies and solutions for the recovery, recycling, and/or reuse of ILs. It is well known that ILs are at least partially miscible with water or hydrocarbons and that leakage into aqueous or non-aqueous environmental compartments is a potential hazard, especially for those ILs that exhibit some degree of toxicity. Most toxicity studies have been conducted against a range of Gram-positive and Gram-negative bacteria and fungi including *Aliivibrio fischeri* (*A. fischeri*), *Escherichia coli* (*E. coli*), *Pseudomonas putida* (*P. putida*), *Staphylococcus aureus* (*S. aureus*), and *Aeromonas hydrophila* (*A. hydrophila*), and the yeasts *Candida albicans* (*C. albicans*) and *Aspergillus niger* (*A. niger*); plants (algae, cereals like barley, wheat, rice, vegetables, eucalyptus, and pine trees); and various aquatic and terrestrial animals (*Daphnia magna* or zebrafish, *Artemia salina*, worms or nematodes) [8]. Therefore, efficient separation and recovery of ILs are important in many chemical, economic, and ecological fields. In the publication by Zhou et al. [9], various methods for the recovery of ILs were discussed in detail and numerous procedures were presented. Although various types of distillation (conventional distillation methods, distillation by reaction of ILs, distillation of ILs as intact ion pairs) and extraction (extraction with water, extraction with organic solvents, extraction with supercritical carbon dioxide) are most commonly used, there is ample room for the use of adsorption (adsorption by activated carbon, adsorption by soils and sediments, adsorption by ion exchange resins), membrane separation (pressure-driven membrane techniques, pervaporation, membrane distillation, electrodialysis), aqueous two-phase extraction (based on addition of chemicals, based on change of temperature), crystallization (solution crystallization, melt crystallization, pressure-induced crystallization), force field (gravity, centrifugation, magnetic field), and even combined methods for recovery of ILs. The higher the recovery, the lower the risk of environmental impact and the more environmentally friendly the process. However, this is not always the case. There are only a very limited number of cases in which significant recovery of ILs has been achieved. Reuse of ILs in repeated experiments is advantageous whenever possible [10–12].

All in all, the potential toxicity of some ILs must be considered and minimized. Is this possible?

It should also be noted that in microextractions, the entire amount of IL used for extraction is usually reused for analysis. After analysis, IL can be found in wastewater, but at highly diluted levels, i.e., low concentrations. However, despite the low concentrations, the cumulative effect should be considered, i.e., the environmental hazard.

Researchers have the task of not only exploring the advantages, but also addressing the disadvantages, shortcomings, and challenges in certain areas. For these reasons, this article addresses several issues that we have registered as lacking in work on ionic liquids (Fig. 1).

Do we need ionic liquids in green analytical chemistry?

Considering that our main goal is to provide useful chemical information, sample preparation is no longer just the bottleneck of the whole analytical process, which cannot be completely avoided, but also a good basis and foundation for improving the analytical method. As analytical chemists, we are tasked with meeting high analytical criteria for good sensitivity/selectivity, reproducibility, accuracy, low limits of detection (LOD) and quantitation (LOQ), and hopefully high robustness of the method we use for measurements. What we can do is to seek and apply “greener” solutions whenever possible. For example, how to handle the reagents and solvents, when they are necessary but, on other hand side not green enough. If toxic organic solvents are unavoidable, decreasing their amounts and recycling for the next use is always a good way. Re-use and avoiding the generation of waste will make them more sustainable. We can replace some organic solvents with ionic liquids in certain cases but, at the same time, to consider their potential toxicity. Between green and white analytical chemistry [6, 7], the main challenge is to find a balance between increasing demands on the quality of results (accuracy, LOD, LOQ, reproducibility, robustness, etc.) and the whiteness of the method, as well as improving environmental friendliness [3–7].

Proper validation of applied method and evaluation of its greenness can produce an outcome of successful bridging. It is common knowledge that the best way to verify that our method works well is to use certified reference materials (CRMs). It is also a fact that CRMs are not available for the vast majority of real samples, so analytical chemists must use other acceptable approaches. If a CRM matrix is at least similar, it can be used, and the results can be compared to other approaches, such as using internal standards or the standard addition method. If the CRM matrix is almost the same and there are no certified values for the compounds we are targeting, this may be useful as additional value for other users of this CRM for interlaboratory comparisons. There were several case studies reported by Wise [13],

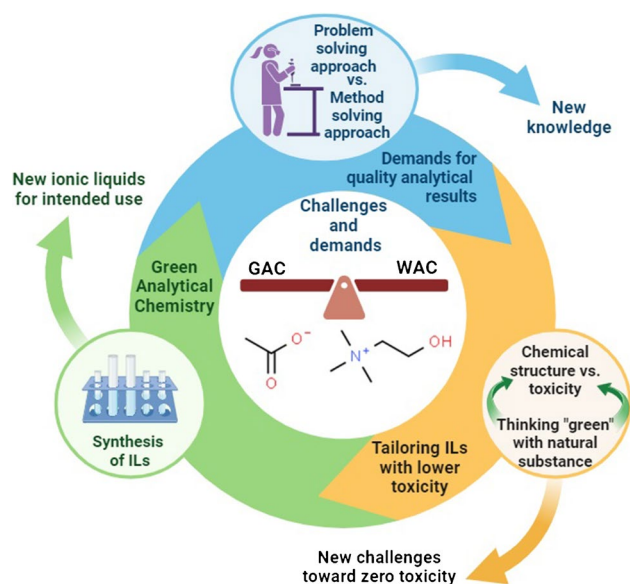


Fig. 1 Ionic liquids—challenges and demands

when NIST (National Institute of Standards and Technology) implemented newly obtained results/methods/analytes for previously uncertified compounds.

In the context of its application, an analytical method is expected to have the widest possible range of linearity, the lowest possible limits of detection and quantification, high reproducibility and accuracy with the lowest possible detection/determination errors, and a high recovery. Validation of newly proposed analytical methods is a critical process designed to demonstrate that a particular method is fit for a particular purpose and provides reliable and accurate results. The validation process usually consists of several phases and includes evaluation of the following parameters: trueness, precision, linearity range, LOD, LOQ, selectivity, robustness, stability, recovery, and enrichment factor.

The results of more than 100 scientific articles (published from 2017 to 2022) developing new sample preparation methods with ionic liquids were analyzed. These methods include techniques such as dispersive liquid–liquid microextraction (IL-DLLME), single-drop microextraction, IL-hollow fiber extraction [14], magnetic IL for liquid–liquid and solid phase extraction [15], IL-based aqueous biphasic systems [3, 16], IL-modified silica gel [17], and nano-IL composites for micro-solid phase extraction [18]. The main focus of these papers is to optimize the experimental conditions in order to achieve the highest possible degree of extraction. Validation of the proposed method was performed in about 80% of these papers that was conducted through the following parameters: determination of LOD and LOQ, linearity range, matrix effect and recovery. For example, very low LOD at the ppt level, high percent recoveries (90–105%), and a wide range of linearity have been

reported for sample preparation methods based on IL. The matrix effect is most often investigated by comparing clean and spike samples and determining recovery. About 60% of the analyzed papers included the repeatability of the proposed method and a comparison with literature data in their validation process. About 20% of the papers addressed selectivity (measurement of the analyte of interest in the presence of potentially interfering compounds) and stability (mainly for protein determination and methods using hollow fiber membranes). Very few papers have done comprehensive validation, including robustness and experimental comparison with another method and the use of CRM (certified reference materials). Is it always the case that “no suitable CRM is available on the market”, or is it just an omission. Samples of natural water or wastewater are still most commonly analyzed using sample preparation methods based on IL (about 40%); however, the number of food (about 25%) and biological samples is increasing (about 25%).

The simplest method for sample preparation using IL is dispersive microextraction (IL-DLLME), which uses very small amounts of IL (20–100 μL). For example, this method was successfully developed and validated for the determination of four aflatoxins in solid flour samples, with detection limits ranging from 0.015 to 0.2 $\mu\text{g kg}^{-1}$ [19]. The choice of IL is crucial in this type of extraction. For example, the task-specific IL allows the selective determination of Cu, Ag, Pd, and Pt in the presence of 15 other metals [20]. Although the extraction conditions for Group 10 (Pd and Pt) and Group 11 (Ag and Cu) elements are usually different, it is possible to combine DLLME and 1-butyl-2-diphenylphosphino-3-methylimidazolium hexafluorophosphate and simultaneously determine these elements with enrichment factors ranging from 14 to 70 and LOD of 0.2–2 $\mu\text{g L}^{-1}$ in a single run. In addition, it was found that the matrix effect disappeared after a sample preparation step based on IL-DLLME. These results suggest that IL-DLLME not only increases the sensitivity of the method but also reduces matrix interference. Given the minimal amounts of IL, the total content of IL is used in further analysis. As a result, IL ends up in the wastewater (e.g., as an eluent in HPLC) after analysis. Although the concentrations of IL in wastewater are very low, it is important to consider that hydrophobic ILs are often toxic and can accumulate after numerous analyses.

Materials modified with ionic liquids have gained considerable importance in sample preparation in recent years. These materials offer distinct advantages, including exceptional selectivity, extremely low limits of quantitation, a high enrichment factor, and can be used multiple times. Dual modification of polystyrene nanofiber mats with IL and polydopamine has proven to be an extremely effective approach for the simultaneous analysis of 15 different mycotoxins in corn and wheat [21]. This remarkable ability can be attributed to the multiple interactions that include hydrogen

bonding, π - π interactions, electrostatic forces, and hydrophobic interactions.

Nano-IL composites for micro-solid phase extraction formed by combining carbon nanomaterials (CNMs), such as carbon nanotubes (CNTs) and graphene, with ILs exhibit exceptional selectivity, sensitivity, and loading capacity [18]. Functionalization of CNTs with IL leads to a change in the CNT surface. For example, when an imidazolium cation is introduced into the CNT surface along with a chloride or tetrafluoroborate anion, the surface becomes hydrophilic. Conversely, if the same imidazolium cation is used together with bis(trifluoromethanesulfonyl)imide or hexafluorophosphate (PF_6^-), the surface becomes hydrophobic. This versatility allows the preparation of novel sorbents tailored to specific analytes or classes of analytes with increased selectivity.

Moreover, the application of covalently bonded IL for graphene oxide as a nanoadsorbent in dispersive solid-phase microextraction has enabled the simultaneous determination of four anabolic steroids and six β -blockers from environmentally relevant aqueous samples [22]. This method achieves LOD in the nanogram per liter range and has high recoveries of 87 to 98%. A comparative study highlights the superior performance of this developed nanomaterial in dispersive micro-solid phase extraction for the extraction of steroids and β -blockers compared to graphene oxide and graphene. While CNMs possess exceptional properties, it is critical to consider their environmental impact when evaluating their “greenness,” as their preparation often requires significant amounts of organic solvents, high temperatures, extended preparation times, and substantial energy consumption.

Tailoring ionic liquids with lower toxicity

Most publications on ionic liquids are concerned with their applicability in sample preparation or/and analysis and their environmental friendliness. What about the amounts of ILs left over and wasted after experiments? In GAC, waste management and environmental impact are paramount.

It is well known that ILs cannot be considered benign a priori, especially because of their high stability, which can make them persistent pollutants, calling into question the environmental friendliness of many ILs [23]. Therefore, it is crucial to assess their potential environmental hazards by determining their persistence in the ecosystem [24], as the hazard posed by ILs can be significant. It was reported by Ventura et al. [25] that imidazolium-based ILs have negative effects on the growth of some microorganisms depending on the anion and alkyl chain length. On the other hand, phosphonium-based ILs do not seem to have negative effects on the longest alkyl chains. It was also found that the alkyl chain, cation structure, and anion component all have significant effects on antimicrobial activity,

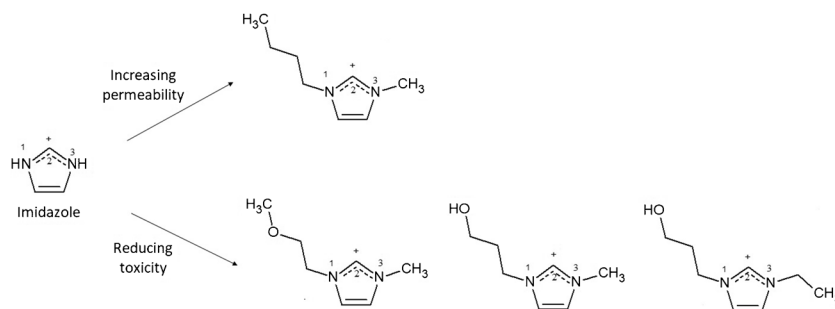
and these effects correlate well with the lipophilicity and thus toxicity of the ILs tested. ILs containing fluoride-based anions such as tetrafluoroborate, hexafluorophosphate, and hexafluoroantimonate are shown to be more toxic than the corresponding alkali salts of these anions. SbF_6^- and PF_6^- were identified as the most toxic anions to *Selenastrum capricornutum*, and the toxicity of imidazolium-based ILs decreases in the following order: $\text{SbF}_6^- > \text{PF}_6^- > \text{BF}_4^- > \text{CF}_3\text{SO}_3^- > \text{C}_8\text{H}_{17}\text{OSO}_3^- > \text{Br}^- \approx \text{Cl}^-$ [26].

There are several approaches to reduce the toxicity of ionic liquids, taking into account that longer alkyl substituents on the heterocyclic structure of the cation increase toxicity of ILs due to better permeability through the cell membrane of living organisms. In some works [27, 28], it was shown that the moderate acute toxicity of imidazolium-based ILs can be significantly reduced by introducing polar groups into the alkyl substituent structure, such as hydroxyl or ether groups. However, the greatest effect on reducing toxicity has shown the introduction of a hydroxyl group into the alkyl chain at the N-1 position of the imidazolium ring, together with an additional extension of the alkyl chain at the N-3 position (Fig. 2).

The second strategy to reduce toxicity and enhanced biodegradability is the synthesis of ionic liquids using naturally derived, environmentally friendly substances (such as choline, amino acids, betaine, agmatine, or vitamins), thus expanding the application of ILs in the pharmaceutical, agricultural, or food industries. Synthesis from nontoxic starting reagents does not necessarily lead to a product with lower toxicity, since the presence of hydrogen bonding acceptors and the ability of the donor significantly affect toxicity [29]. The toxicity of vitamin-based ILs containing choline as a cation and ascorbate, biotinate, or nicotinate anions was determined in a human nontumor cell line (normal fetal lung fibroblasts MRC-5) and H-4-IIIE (rat liver hepatoma) [30]. The results showed that the ionic liquid of choline ascorbate is significantly less toxic than the starting component ascorbic acid.

New-generation protic (PILs) and zwitterionic liquids (ZILs) have also recently attracted the attention of scientists, but information on their toxicity is still lacking in the literature. Unlike conventional aprotic ionic liquids, PILs consist of proton-donating cations and proton-accepting anions [31]. Their low cost, miscibility with polar and non-polar solvents, stability under normal conditions, and simple one-step synthesis based on an acid–base reaction between a Brønsted acid and a Brønsted base make them more attractive for various procedures and applications. It is very likely that the toxicity characteristics are highly dependent on the choice of Brønsted acid and base, and a case-by-case evaluation is required to determine their safety for a particular use. The studied toxicity of PILs containing amino alcohol- or choline-based cations exhibits moderate or high toxicity to microorganisms (e.g., fungi or bacteria) but are not

Fig. 2 Chemical structures of the imidazolium-based cations with different toxicity



toxic or are only slightly toxic to humans. This property was observed by Dimitrić et al. in the case of 1-amino-2-propanol-based PILs, as the amino alcohol studied was shown to have no toxic effect on humans [32]. Based on the natural origin of the anions, the toxicity of PILs can also be tuned and reduced [33]. A detailed evaluation of the hazard assessment of PILs by Peric et al. [34] shows that these ionic liquids have EC_{50} values above 100 mg/dm^3 in most of the tests performed and that they are readily biodegradable. The EC_{50} values for aprotic ILs are several orders of magnitude lower than those for protic ILs, suggesting that PILs can be considered as a more environmentally friendly alternative to aprotic and conventional ILs and volatile organic solvents.

On the other hand, zwitterionic liquids are a subclass of ionic liquids characterized by the presence of both cationic and anionic functional groups covalently bonded in the same molecule with a total charge equal to zero. This complexity indicates that their ecotoxicological behavior probably should not be extrapolated from known facts about widely used aprotic ionic liquids [35]. Sixteen ZILs containing ammonium, imidazolium, pyridinium, pyrrolidinium, and piperidinium cations and sulfonate or carboxylate anions were studied by Jesus et al. and all ZILs studied were reported to be harmless and to have significantly lower hazard potential to aquatic species than the corresponding aprotic ionic liquids. As the hydrophobicity of the cation increases, the toxicity to microalgae increases, but no significant differences were found when considering the different cationic groups of the hermaphroditic ionic liquids studied, in contrast to what is known for the ecotoxicity of ionic liquids.

Drawing conclusions

For ionic liquids, non-molecular compounds with unique physicochemical properties, “fit to purpose” means to exploit their enormous potential, designing and applying them and being aware of their advantages and disadvantages. In line with current trends, the main challenge will continue to be finding a balance between the increasing requirements for quality of results (accuracy, LOD, LOQ, reproducibility, robustness, etc.) contained in twelve principles of white

analytical chemistry (WAC) and the improvement of environmental friendliness contained in the twelve principles of green analytical chemistry (GAC). There is no 100% green analytical method or procedure, but proper method validation is essential. Analysis of various samples (mostly environmental, food, and less biological samples) with an IL-based sample preparation, briefly presented in this article, included a proper method validation and very low LOD values, high recoveries, and reduced matrix interferences.

Toxicity as an inherent property of some ionic liquids is addressed in this article. Reducing the environmental risk of ionic liquids and improving their biodegradability are possible by (i) understanding the relationship between chemical structure and toxicity and (ii) using of naturally derived, nontoxic substances. The evaluation of the toxicity of the new-generation protic and zwitterionic liquids also shows that they can be used as less harmful and less hazardous reagents compared to the commercially produced and widely used aprotic ionic liquids.

In summary, a multidisciplinary approach to ionic liquid-based applications that considers analytical chemistry first, toxicology, and ecology is essential for better analytical protocols and a healthier environment.

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Declarations

Conflict of interest The authors declare no competing interests.

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