Misuse of sustainability concept may lead to even more toxic chemical materials

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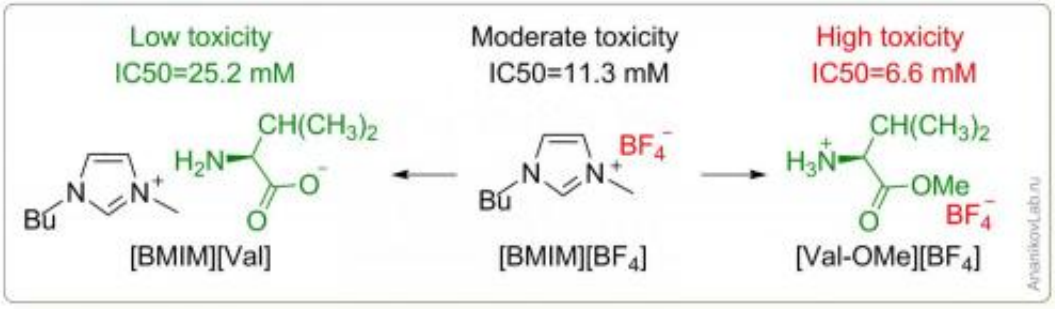


Introduction of amino acid into ionic liquid may help to achieve the desired goal – to decrease toxicity. However, in a certain case, this will change the system into opposite direction and will substantially increase toxicity. (IC50 - half maximal inhibitory concentration; the smaller the value – the higher the toxicity of the chemical compound). Credit: Zelinsky Institute of Organic Chemistry

Replacement of toxic chemical components by nontoxic and biocompatible natural analogs is one of the most popular approaches in sustainable projects. A study carried out at Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (Moscow) has shown that partial replacement of chemical compounds by their natural analogs may surprisingly lead to even more toxic products. The article published in *Toxicology Research* describes increased toxicity of ionic liquids after incorporation of amino acid residues.

The 21st century has presented us with a new scientific challenge -

sustainable development. In a battle for a sustainable world, humanity seeks to achieve such noble goals as creating a new generation of superior chemical technologies and materials with complete environmental compatibility.

Chemistry belongs to the sciences for which the concept of nontoxic and waste-free production is of greatest importance. Principles of green chemistry and sustainability have largely influenced research and development in chemical sciences. These principles include convenient degradability and minimized toxicity. It is a well known fact that common chemicals are mainly based on toxic, bioincompatible substances that are dangerous for the environment. On the contrary, natural components are biocompatible and have no toxic effects. Nowadays, chemists undertake numerous efforts to replace toxic substances with corresponding natural analogs, and fortunately, change of just one component sometimes does increase environmental compatibility and reduces harmful impact.

This approach has been used in attempts to create biocompatible ionic liquids. Ionic liquids, also called molten salts, liquid electrolytes, or ionic melts, are salts that are liquid at temperatures below 100ºC. Spatial directionality and segregated nano-structuring found in ionic liquids provide them with unique properties, one of the most startling of which is the possibility of 'fine-tuning.' Each ionic liquid consists of cation and anion moieties, and by varying them, individually or together, certain properties of the IL can be changed.

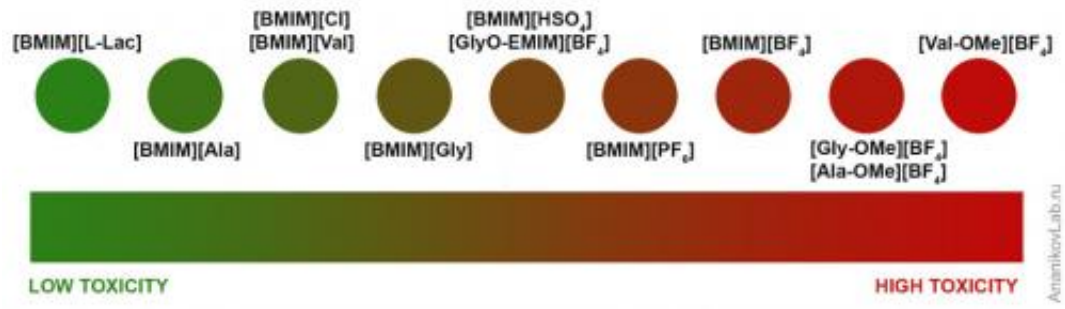
Being nonvolatile and nonflammable substances, ionic liquids were once believed to present a replacement to traditional volatile and flammable organic solvents, and have found application in such various fields of modern chemistry and technology as organic synthesis, catalysis, electrochemistry, nuclear fuel processing, and others. Originally, ionic liquids were considered as 'green' chemicals; however, their biological

potential has quickly become evident. Now it is established that ionic liquids may affect life at all levels, from single biomolecules to whole ecosystems.

The study carried out by researchers from the Zelinsky Institute of Organic Chemistry evaluates the activity of a recently developed class of amino acid-containing ionic liquids towards cancerous and normal cell cultures. In agreement with the above-mentioned sustainability considerations, it was taken for granted that introduction of a natural component (i.e. amino acid) into the ionic liquid would decrease its toxicity and lead to more environmentally friendly chemical derivative.

The researchers replaced the cation and anion in the common ionic liquid [BMIM][BF4] with the natural amino acid Valine to obtain two modified ionic liquids - [BMIM][Val] (bearing Valine as an anion) and [Val-OMe][BF4] (bearing valine as a cation). As one may expect, [BMIM][Val] turned out to be less toxic than the original compound [BMIM][BF4] (see Figure 1). However, [Val-OMe][BF4] demonstrated unexpectedly high toxicity. Surprisingly, replacement of chemical component [BMIM]+ with a natural cation based on valine gave noticeably more toxic ionic product.

The authors tested a series of common and amino acid-based ILs and showed that ionic liquids containing anions or cations based on the amino acids glycine, alanine, or valine generally demonstrate cytotoxicity higher or comparable to that of conventional imidazolium-based ILs with inorganic or small organic anions (Figure 2). The authors observed increased toxicity for several ionic systems after incorporation of natural amino acid fragments.



Cytotoxicity of ionic liquids containing amino acid residues on the relative low and high toxicity scale. Credit: Zelinsky Institute of Organic Chemistry

A possible mechanism of action of such amino acid containing ionic liquids involves interactions with membrane transporter proteins employed by cells for amino acid intake. A harmless amino acid, being a part of ionic liquid, helps a biologically active/toxic moiety to enter the cell, where it causes apoptosis, or programmed cell death. Although the original goal of making a nontoxic ionic liquid was not achieved, these findings suggest potential application of amino acid containing ionic liquids in biology and medicine for targeted drug delivery utilizing tunable properties of ionic liquids.

As Prof. Ananikov commented: "Toxicity and eco-activity of ionic liquids is now a well-addressed topic. As we recently reviewed, achieving superior chemical properties, as well as simultaneously holding environmental compatibility, is a very complicated, but unavoidable direction for task-specific optimization."

More information: "Unexpected increase of toxicity of amino acid-containing ionic liquids." *Toxicol. Res.*, 2015, 4, 152-159, DOI: 10.1039/C4TX00079J

"Toxicity of Ionic Liquids: Eco(cyto)activity as Complicated, but

Unavoidable Parameter for Task-Specific Optimization", *ChemSusChem*, 2014, 7, 336-360. DOI: 10.1002/cssc.201300459