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How the structure of ionic liquid affects its toxicity to *Vibrio fischeri*?

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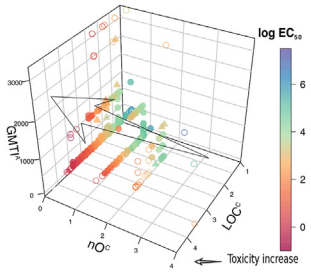
HIGHLIGHTS

- We proposed a QSAR model predicting the toxicity of ionic liquids to *Vibrio fischeri*.
- Effect of the cation and anion structures on the modeled property was determinated.
- The toxicity of ILs depends mostly on the cation's structure – its size and length.
- The presence of polar groups in the cation's reduces the toxic properties of ILs'.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present work, we have proposed a statistical model predicting the toxicity of ionic liquids (ILs) to *Vibrio fischeri* bacteria using the Quantitative Structure-Activity Relationships (QSAR) method. The model was developed with Multiple Linear Regression (MLR) technique, using the Gutman molecular topological index (GMTI), the lopping centric information index (LOC) and the number of oxygen atoms. Presented model is characterized by the good fit to the experimental data ($R^2 = 0.78$), high robustness ($Q^2_{CV} = 0.72$) and good predictive ability ($Q^2_{EXT} = 0.75$). This approach, with using very simple descriptors, helps to initially evaluate the toxicity of newly designed ionic liquids. The studied toxicity of ionic liquids depends mainly on their cations' structure: larger, more branched cations with long alkyl chains are more toxic than the smaller, linear ones. The presence of polar functional groups in the cation's structure reduces the toxic properties of ionic liquids. The structure of the anion has little effect on the toxicity of the studied ionic liquids. Obtained results will provide insight into the toxicity mechanisms and useful information for assessing the potential ecological risk of ionic liquids.

1. Introduction

The ionic liquids (ILs) have several characteristic properties, which make them a very unique class of chemicals. These are for example: low vapor pressure (Aschenbrenner et al., 2009), high thermal stability (up to temperatures of 450 °C) (Endres and Zein El Abedin, 2006) and melting point below 100 °C. Moreover, majority of ILs are in liquid state at the room temperature (Endres and Zein El Abedin, 2006). ILs are usually built of a large organic cation (e.g. ammonium, imidazolium, pyridinium, pyrrolidinium, quinolinium, piperidinium, morpholinium cation) and a smaller, inorganic anion (e.g. bromide, iodide, chloride, tetrafluoroboranuide, hexafluorophosphate). Rarely, organic anions might be bigger, as for example in bis(trifluoromethylsulfonyl)amide. A large number of different combinations between cations and anions allows creating chemical compounds with various chemical properties and, by that,

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with variable applications (Torrecilla et al., 2009) in many areas of science and technology. Ionic liquids are widely used in electronics (e.g., batteries, solar panels, fossil fuels (MacFarlane et al., 2014)), agriculture (e.g., herbicides (Pernak et al., 2013), cellulose derivatives (Domínguez de María, 2014)) and in the chemical analytics as well (Sun and Armstrong, 2010).

For a long time ionic liquids have been considered as "green solvents" – safe for human and for the environment (Das and Roy, 2012, 2013; Dukhande et al., 2013). However, in recent years their (eco-)toxicological potential has been demonstrated. One of the most significant threats related to the use of ILs comes from their high solubility in water, which enhances their dispersion into aquatic systems. Therefore, there is a strong need to recognize and explore their eventual influence on living organisms in spite of their accidental leak out into the environment (Torrecilla et al., 2009). There are many studies on ILs' ecotoxicity with use of different organisms, such as bacteria *Vibrio fischeri* (Ranke et al., 2004), small crustaceans *Daphnia magna* (Bernot et al., 2005; Samorì et al., 2007), duckweed *Lemna minor* (Stolte et al., 2007), *algae Oocystis submarina* (Latala et al., 2009b). In addition, toxic activity of ILs was examined with using of inhibition of *a*cetylcholinesterase (AChE) (Stock et al., 2004) cell viability assay with leukemia rat cell line (IPC-81) (Ranke et al., 2004). Previous contributions demonstrated examples of the strong relationships existing between the structure of ILs and their toxicity (Sosnowska et al., 2014). It is worth mentioning that toxicity of ILs depends in most cases on their lipophilicity (Latala et al., 2009a) and increases with the increasing alkyl chain length (Ranke et al., 2004; Samorì et al., 2007; Stasiewicz et al., 2008; Viboud et al., 2012; Sosnowska et al., 2014). In this context, the presence of polar groups in the cation (mainly containing oxygen or nitrogen atom) results in a decrease of the toxic properties (Viboud et al., 2012).

From environmental point of view, there is a significant need to determine a comprehensive risk assessment for all groups of ionic liquids. Unfortunately, the number of possible cation-anion combinations is extensive. For such a large number of chemical compounds, empirical toxicity measurement is impossible, due to time limitation and high cost of the analytical procedures. Therefore, alternative methods for predicted the toxicity of ILs are required.

In this work, we have investigated which structural properties of ILs are responsible for their toxicity against *Vibrio fischeri* by employing the computational Quantitative Structure-Activity Relationship (QSAR) modeling. The model, computationally developed within this work, enables predicting the missing values of the toxicity for selected ILs. Conclusions from our work would be further used for preliminary evaluation of the toxicity of newly designed ionic liquids.

2. Material and methods

The QSAR model was developed according to the following scheme: (i) collecting experimental data, (ii) calculating molecular descriptors, (iii) splitting the dataset into training and validation subsets, (iv) determining the relationship between the structure and activity, and (v) validating the developed model.

2.1. Dataset

The experimental data of ILs' toxicity against bacteria *Vibrio fischeri* – bioluminescence inhibition (measured as the 30 min EC_{50} [μM]) were taken from the literature (Stolte, 2003; Ranke et al., 2004; Stolte et al., 2007) and transferred into logarithmic units. Every experimental data point was measured in the same conditions, using the same procedure. The collected dataset contained the toxicity values for 56 ionic liquids, composed with 4 different types of cations (imidazolium, ammonium, pyridinium and pyrolidinium) and 15 types of anions: chloride, bromide, iodide, tetrafluoroboranuide, hexafluoridophosphate, acetate, O-octyl sulfate, O-ethyl sulfate, 4-methylbenzenesulfonate, hydroxyacetate, 1,1-dioxo-1,2-dihydrobenzo[*d*]isothiazol-3-onate(1-)m, bis[1,2-benzenediolato(2-)]borate, bis(pentafluoroethyl)phosphinate, bis(trifluoromethylsulfonyl)amide(1-), sulfamate and bis(trifluoromethyl)amide(1-) (Table 1). For detailed information about the collected toxicity values please refer to the Table ES1 in Electronic Supplementary Material. The experimental data with critical evaluation according to Klimisch criteria are also available in our online ILsTOX database (www.db.qsar.eu.org).

2.2. Descriptor calculation

The three-dimensional molecular models of the studied ionic liquids were constructed with use of ChemSketch software (Inc, 2014). For the purpose of further analysis, cations and anions were built up separately.

Molecular geometry of each molecular model was optimized at the semi-empirical PM7 level using MOPAC 2012 software (Stewart, 2012). It has been already proven that semi-empirical methods can be successfully used in QSPR/QSAR modeling at the stage of ILs' geometry optimization (Rybinska et al., 2016). Based on the earlier studies, which demonstrated that the toxicity of ionic liquids depends on their structure (Stasiewicz et al., 2008; Ventura et al., 2012; Viboud et al., 2012; Sosnowska et al., 2014), we preselected five groups of molecular descriptors to be calculated and employed for developing the QSAR model, namely: (i) Weighted Holistic Invariant Molecular Descriptors (WHIM), (ii) ring descriptors, (iii) functional group counts, (iv) topological and (v) constitutional indices. The descriptors (221 descriptors in total for anion and 208 descriptor for cation) were calculated with Dragon 6 software (Talete, 2014).

2.3. Splitting data

In the next step, the ionic liquids from the dataset were sorted according to the increasing values of log EC_{50}, and the dataset was split into two smaller subsets: training and validation (test). The splitting was performed using a "Z:1 algorithm", according to which, after sorting, every *Z-th* compound (in our work $Z = 4$) was put into a validation set (Puzyn et al., 2011). Additionally, as most of the compounds in dataset were imidazolium ILs, we decided that at least one IL from every group should be present in both training and validation sets. The ionic liquids with the extreme (highest and lowest) toxicity values were included in the training set. Thus, we obtained a training set with 42 (75%) compounds and a validation set with 14 (25%) ILs. The dataset splitting outcome specifics are presented in Table ES1 in Electronic Supplementary Material section.

2.4. Descriptors selection

Genetic Algorithm (Haupt and Haupt, 2004) implemented in the QSARINS 2.2 software (Gramatica et al., 2013, 2014) was used to select the most optimal combination of descriptors for QSAR modeling. The following control parameters for genetic algorithm were used: population size: 100, mutation rate: 50%. Three descriptors selected this way were utilized in the Multiple Linear Regression (MLR) model development.

2.5. Validation of the developed model

The goodness-of-fit of the developed model was measured by