Chemosphere 159 (2016) 178–183

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Interpretation of toxicological activity of ionic liquids to acetylcholinesterase inhibition via *in silico* modelling

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HIGHLIGHTS

- Toxicological interactions between ionic liquids (ILs) and acetylcholinesterase activation are explained in molecular basis.
- *In silico* calculated LFER descriptors can well correlate with toxicity values of ILs.
- H-bonding acidity of IL cation has the most contributing factor to enzyme activity inhibition.
- Enzyme inhibition is caused by different toxicological interactions from other responses to IL toxicity.

ARTICLE INFO

Article history:
Received 9 March 2016
Received in revised form
24 May 2016
Accepted 1 June 2016
Available online 10 June 2016

Handling Editor: I. Cousins

Keywords:
Ionic liquids
LFER
Toxicity
QSAR
Molecular interactions

ABSTRACT

For designing environmentally friendly ionic liquids (ILs), their structural effects on the toxicity should be interpreted via modelling based on the quantitative-structure-activity-relationship (QSAR) concept. For the purpose, QSAR models for predicting IL toxicity in acetylcholinesterase activity were developed by using linear free-energy relationship (LFER) descriptors, whose chemical meanings are well defined. These are excess molar refraction ($E_{c\ or\ a}$), dipolarity/polarizability ($S_{c\ or\ a}$), H-bonding acidity ($A_{c\ or\ a}$), H-bonding basicity ($B_{c\ or\ a}$), McGowan volume ($V_{c\ or\ a}$), and ionic interactions of cation (J^+) and anion (J^-). Since the experimentally determined LFER descriptors are not available, we calculated them based on density functional theory, conductor-like screening model and the open-source software, obprop. The toxicity values of imidazolium- and pyridinium-based ILs could be predicted by a combination of four descriptors (A_c, B_c, V_c and S_a) with an R^2 of 0.828, and (E_c, A_c, E_a and S_a) with an R^2 of 0.879, respectively. In prediction study using the overall dataset containing various IL structures, the six calculated terms (E_c, S_c, A_c, J^+, E_a, and S_a) were selected and correlated with the observed toxicity values in R^2 of 0.748 for the training set, R^2 of 0.711 for the test set and R^2 of 0.655 for external validation set. And this study explains how the selected terms are contributing to the prediction models, and their chemical meanings were understood.

1. Introduction

Modelling based on the quantitative-structure-activity relationship (QSAR) concept aims to find the relationship between chemical structure and its physicochemical property in medicinal chemistry, environmental assessment and material sciences (Roy et al., 2015a; Dearden, 2016). This method facilitates investigation of numerously existing or only theoretically existing chemicals because of its rapid screening and structurally analyzing abilities for chemicals. Moreover, it is safer and less expensive compared to experimental approaches. In this study, this theoretical method was applied to predict the toxicological effects of ionic liquids (ILs), which have been highlighted in IL related research fields.

ILs can play roles as electrolytes, catalysts, extractants and lubricants in many applications. Due to the structural tunability of ILs, their physical and chemical properties can be controlled, which facilitates their exploitation in the chemical industries (Plechkova and Seddon, 2008). However, from an environmental viewpoint, these properties can result in various toxicological effects to various environments if they are released into nature. Indeed, negative environmental aspects of ILs on the environment have been reported (Amde et al., 2015; Bubalo et al., 2014; Egorova and Ananikov, 2014; Kudłak et al., 2015; Pham et al., 2010; Ranke et al., 2007). Accordingly, the toxicity of ILs should be

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http://dx.doi.org/10.1016/j.chemosphere.2016.06.005
0045-6535/

characterized before their applications for the safe use.

However, experimental toxicity measurements are restricted by availability of time and materials. Such approaches may not cover all types of ILs towards numerous toxicity testing methods. Therefore, a theoretical approach is advisable. Indeed, theoretical approaches have been be successfully applied to prediction of IL toxicity towards water flea (Cho and Yun, 2016; Couling et al., 2006; Hossain et al., 2011; Roy and Das, 2013, 2014, 2015b; Sosnowska et al., 2014; Wang et al., 2015), bacteria (Cho et al., 2013, 2016; Luis et al., 2010; Bruzzone et al., 2011; Sosnowska et al., 2014), animal cells (Cho et al., 2013; Sosnowska et al., 2014; Torrecilla et al., 2009; Yan et al., 2012a; Fatemi and Izadiyan, 2011; Garcia-Lorenzo et al., 2008), enzymes (Sosnowska et al., 2014; Torrecilla et al., 2009; Yan et al., 2012b; Basant et al., 2015; Das and Roy, 2014a) and algae (Cho et al., 2013; Das and Roy, 2014b).

Among toxicity testing methods, the acetylcholinesterase enzyme inhibition test is important because it assesses acetylcholine hydrolysis to acetate and choline in human neurons. Its inhibition damages human neuronal processes. To date, the toxicity values of ~300 ILs have been reported by the several research groups. This enables QSAR modelling to be challenged. The following attempts have been reported. An initial trial correlated the lipophilicities of cations with toxicity values using 24 data points, and found a linear relationship with an R^2 of 0.794 (Arning et al., 2008). In 2009, Torrecilla et al. (2009) predicted the values using empirical formulae; e.g., numbers of atoms (including C, H, N, O, P, and F), number of rings, number of benzene rings and molecular weight based on multiple linear regression (MLR), neutral network (NN), radial basis network (RB) and multilayer perceptron (MLP). The developed models had R^2 values of 0.814–0.973. Yan et al. (2012b) reported a model based on a topological index; e.g., atomic van der Waals radii, atomic radius, and atomic electronegativity, together with the toxicity values of 221 ILs. Its predictability was evidenced by an R^2 of 0.877 and SE of 0.153 log unit. With the same approach, Das and Roy (2014a) developed a model with R^2 of 0.918 (training set) and 0.861 (test set). Peric et al. (2015) developed a model for aliphatic protic ILs using the group contribution method. Basant et al. (2015) suggested nonlinear models based on machine-learning approaches; i.e., cascade correlation network (CCN) and support vector machines (SVMs). However, some former models have some shortcomings and must be updated when a new class of IL is introduced. Actually, the physicochemical meanings of the models are not explicit and they have a number of parameters; these obscured to understand the toxicological interactions of ILs with enzyme activities. Therefore, an easily understandable and simple model should be established to support design of environmentally benign chemical structures.

For this purpose, a linear free energy relationship (LFER) model is suitable because it consists of a few descriptors with well-defined physicochemical meanings (Abraham and Acree, 2016). The model is shown as Eq. (1).

$$\mathbf{SP} = e\,\boldsymbol{E} + s\,\boldsymbol{S} + a\,\boldsymbol{A} + b\,\boldsymbol{B} + v\,\boldsymbol{V} + j^{-}\boldsymbol{J}^{-} + j^{+}\boldsymbol{J}^{+} + c \quad (1)$$

where SP stands for solute property. The capital letters (*E, S, A, B, V,* J^-, and J^+) indicate solute descriptors and small letters (*e*, *s*, *a*, *b*, *v*, j^-, j^+, and *c*) do system parameters. In capital letters, *E* [$cm^3\ mol^{-1}$/10] means excess molar refraction due to interaction of *n*- or *pi*-electronic lone pair of molecules; *S* [dimensionless] indicates dipolarity/polarizability by dipole-dipole and dipole-induced dipole interactions; *A* and *B* [dimensionless] are hydrogen bonding acidity and basicity, respectively; *V* [$cm^3\ mol^{-1}$/100] is the McGowan volume of the atom or molecule; and J^- and J^+ [dimensionless] stand for ionic interactions of anion and cation, respectively. However, the experimentally determined LFER descriptors of IL ions are not available so far. Therefore, they were calculated by using *in silico* calculations (see 2.2. computational in detail in experimental section). Here, for *in silico* calculation of toxicity values, we computed the descriptors, based on our previous study, (Cho et al., 2015) using density functional theory (DFT) (Parr and Yang, 1989), conductor-like screening model (COSMO) (Klamt and Schüürmann, 1993), and the obprop internet freeware (O'Boyle et al., 2011).

In this study, we aimed to develop predictive LFER models for ILs' inhibition ability to acetylcholinesterase activity and to identify the main toxicological interaction potentials. For interpretating the structural effects of ILs on their toxicity, the calculated LFER descriptors were applied to predict toxicity values of imidazolium-based ILs, pyridinium-based ILs and overall data set containing several IL structures. And from the developed linear LFER models, the mechanism of interactions bewteen ILs' toxicity and acetylcholinesterase activity were explained and compared with those in other biological responses to IL toxicity.

2. Materials and methods

2.1. Database of ionic liquids and their abbreviations

For the establishment of prediction model, 253 experimentally determined 50% effective concentration (EC_{50}) values of ILs of acetylcholineasterase activation were collected from the literatures (Ranke et al., 2007; Torrecilla et al., 2009; Stasiewicz et al., 2008; Centre for Environmental Research and Sustainable Technology (UFT)), which are log unit in the μM. The collected ILs comprised eight head groups of imidazolium (IM), ammonium (N), pyridinium (Py), pyrrolidinium (Pyr), phosphonium (P), piperidinium (Pip), quinolinium (Quin) and morpholinium (Mor) with several functional groups and substitutions, and various anions. The abbreviations of IL ions and log $1/EC_{50}$ values are provided in the supporting information (Supporting information 2 as excel file).

2.2. Computational details

Sub-parameters for calculating the LFER descriptors were computed using DFT (Parr and Yang, 1989) and COSMO (Klamt and Schüürmann, 1993). The calculation environment was in the TURBOMOLE V5.10 program package (2008). Initially, (RI-)BP86/SV(P) (Schäfer et al., 1992; Becke, 1988; Vosko et al., 1980; Perdew, 1986) optimizations for IL ions with the assumption of a gas phase were carried out, and then their vibration frequencies were calculated using AOFORCE (Deglmann and Furche, 2002; Deglmann et al., 2002). Next, the ionic structures were further refined using the TZVP basis set (Schäfer et al., 1994), and then a full optimization was performed again using the TZVP basis set (Schäfer et al., 1994) and COSMO (Klamt and Schüürmann, 1993). From the calculations,.ccf files of ILs ions were produced and sent to COSMO-RS (Eckert, 1999–2014) to generate the sub-parameters based on BP_TZVP_C21_0108 parameterization.

The conversion of the calculated sub-parameters to LFER descriptors was explained in detail by Cho et al. (2015). The calculated values of the descriptors are given in supporting information 2.

2.3. Statistical methods

Multiple linear regressions were performed using SPSS 12.0.1 for Windows, and linear regression was fitted by SigmaPlot for Windows version 10.0.