Journal of Hazardous Materials 311 (2016) 168–175

Contents lists available at ScienceDirect

Journal of Hazardous Materials

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

Modelling for antimicrobial activities of ionic liquids towards *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* using linear free energy relationship descriptors

Chul-Woong Cho[a], Jeong-Soo Park[a], Stefan Stolte[b,c,**], Yeoung-Sang Yun[a,*]

[a] School of Chemical Engineering, Chonbuk National University, 567 Beakje-dearo, Deokjin-gu, Jeonju, Jeonbuk 561-756, Republic of Korea, Republic of Korea
[b] Centre for Environmental Research and Sustainable Technology (UFT), University of Bremen, Leobener Straße, 28359 Bremen, Germany
[c] Department of Environmental Analysis, Faculty of Chemistry, University of Gdańsk, ul.Wita Stwosza 63, 80-308 Gdańsk, Poland

HIGHLIGHTS

- Prediction models were developed for ILs toxicity to two bacteria and a fungus.
- Antimicrobial activities of ILs can be well explained by LFER descriptors.
- IL cation has more toxic impact than anion in antimicrobial activities.
- *E. coli* and *S. aureus* are sensitive to molecular volume of cation.
- *C. albicans* is sensitive to dipole interactions and H-bonding basicity of cation.

ARTICLE INFO

Article history:
Received 13 November 2015
Received in revised form 26 February 2016
Accepted 3 March 2016
Available online 9 March 2016

Keyword:
LFER
Ionic liquids
Toxicity
Prediction
Antimicrobial activity
DFT
Conductor-like screening model

ABSTRACT

To predict antimicrobial activities *i.e.*, minimal inhibitory concentration (MIC) and minimal biocidal concentration (MBC) for ionic liquids (ILs) against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*, six quantitative structure-activity relationship (QSAR) models were developed using linear free energy relationship (LFER) descriptors calculated by density functional theory and conductor screening model. The LFER descriptors are excess molar refraction, dipolarity/polarizability, H-bonding acidity, H-bonding basicity, McGowan volume, cationic interaction, and anionic interaction. By excluding some descriptors with ignorable contributions to training set, components of the QSAR models were simplified. Their estimated predictabilities were in $R^2 = 0.900$, standard error (SE; in log unit of μM) = 0.430 for log 1/MIC of *E. coli*, $R^2 = 0.934$, SE = 0.370 for log 1/MBC of *E. coli*, $R^2 = 0.910$, SE = 0.470 for log 1/MIC of *S. aureus*, $R^2 = 0.947$, SE = 0.350 for log 1/MBC of *S. aureus*, $R^2 = 0.892$, SE = 0.362 for log 1/MIC of *C. albicans* and $R^2 = 0.803$, SE = 0.233 for log 1/MBC of *C. albicans*. Then, except for log 1/MBC of *C. albicans* due to lack of data points, the models were validated by comparing between observed and calculated values of test set; its checked correlations were all within R^2 of 0.921.

1. Introduction

Ionic liquids are molten salts comprised of an organic cation and a weakly coordinating anion [1]. Some have excellent properties such as low melting point, ignorable flammability, low vapor pressure, and favorable solvating ability for a wide range of polar and non-polar materials. By modifying the chemical structures of the cation and the anion or by changing their combination, physicochemical properties of ILs can be appropriately controlled for a wide range of industrial applications such as surfactant [2], catalyst [3], electrolysis [4], and dissolvent [5]. Another remarkable advantage of ILs is that they can support environment-friendly process, not causing severe atmospheric pollution unlike the traditional organic solvents [6].

In parallel with the rapidly expanding knowledge about ILs (> 50 000 publication can be found [7]), more and more data on their (eco) toxicology, biodegradability and environmental fate is becoming available and several hundred papers have recently been published on this aspect. For example researchers tested toxicity values of IL towards aqueous organisms *e.g.*, bacteria [8–19], human cells [20],

* Corresponding author.
** Corresponding author.
E-mail addresses: stefan.stolte@uni-bremen.de (S. Stolte), ysyun@jbnu.ac.kr (Y.-S. Yun).

http://dx.doi.org/10.1016/j.jhazmat.2016.03.006
0304-3894/

Leukemia rat cells [21–23], and various aquatic organisms including algae [24–33], *Lemna minor* [34], fresh water snail *Physa acuta* [35], freshwater crustacean *Daphnia magna* [36], and zebra fish *Danio rerio* [37]. The biodegradability of ILs according to chemical structures was examined by several researchers [38–45]. The detailed information on biodegradation and toxicity of ILs is provided in review articles [36–50]. Based on these studies, we now know that ILs have a wide range of hazard potential as expected and the (eco) toxicological effects of ILs strongly depends on their chemical structures.

Computer-aided calculations are essential for effective studies on the numerous ILs' chemical structures. Indeed, *in silico* methods are safer, faster, more reproducible, and more cost effective than experimental ones, and its predicted value is equivalent to experimental ones as stated by the European Union Regulation on Chemical Substances REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) [51]. Thus, several researchers have established predictive models for the toxicological effects of ILs towards acetylcholinesterase [52], *leukemia* rat cells [53,54], algae [55], and *Vibrio fischeri* [56]. However, so far there is no predictive model towards antimicrobial activities *i.e.,* minimal inhibitory concentration (MIC) and minimal biocidal concentration (MBC) of diploid fungus *Candida albicans* (*C. albicans*), Gram negative rod *Escherichia coli (E. coli)* and Gram positive cocci *Staphylococcus aureus* (*S. aureus*), except simple correlations with calculated octanol-water partitioning coefficient (log P) and determined lipophilicity (log *k*) [9]. The correlations of log P and log *k* with log 1/MIC towards *E. coli* and *S. aureus* are within R^2 of 0.74 and R^2 of 0.60, which are rather poor agreements.

The possibility to predict the antimicrobial and antifungal activities of ILs is important for two different aspects. The antimicrobial activity of ILs to pathogenic microorganisms could be used in medical preparations – here a rational design of ILs with high biological activity is needed. For most other application and in context of a low risk to human and the environment, low antimicrobial activities are favorable. In these points of view, QSAR/QSPR model is advantageous for appropriate selection or design of ILs in effective way. Therefore, in the present study, we developed robust and precise prediction models for log 1/MIC and log 1/MBC for ILs to *E. coli*, *S. aureus* and *C. albicans* using calculated linear free energy relationship (LFER) descriptors.

2. Materials and methods

2.1. Background of linear free energy relationship model

LFER model [Eq. (1)] has been used to develop QSAR/QSPR model of atom or molecules because it is helpful to understand chemically interactive mechanisms caused by the composition of a few number of descriptors which have well-defined physicochemical meanings [57]. Actually, the applicability of LFER descriptors was shown by predicting physicochemical properties of chemicals as a solute [58]. The equation is as follows:

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

where, SP is the solute property. The capital letters are solute descriptors: E – excess molar refraction due to interaction of *n*- or *pi*- electron lone pairs of the molecules, S – dipolarity/polarizability by dipole–dipole and dipole-induced dipole interactions, A – hydrogen bonding acidity, B – hydrogen bonding basicity, V – McGowan volume, J^- and J^+ are ionic interactions of the anion and the cation, respectively. The small letters (*e*, *s*, *a*, *b*, *v*, j^-, j^+, and *c*) stand for system parameters. For general explanations and applications, we recommend a review paper by Poole et al. [58]. And more details on ionic terms (J^+ and J^-) are given in refs 59–62.

Since ILs are generally dissociated in the aqueous phase, study of the activity of the individual ions is needed. Thus, we extended Eq. (1) to Eq. (2) for addressing the individual behaviors of the cation and the anion.

$$\text{Log}\,[1/\text{MIC and MBC}]\ \text{in log unit of}\ \mu\text{M} = e_c\mathbf{E}_c + s_c\mathbf{S}_c + a_c\mathbf{A}_c + b_c\mathbf{B}_c + v_c\mathbf{V}_c + j^{+}\mathbf{J}^{+} + e_a\mathbf{E}_a + s_a\mathbf{S}_a + a_a\mathbf{A}_a + b_a\mathbf{B}_a + v_a\mathbf{V}_a + j^{-}\mathbf{J}^{-} + c \quad (2)$$

where, the solute property is log [1/MIC and 1/MBC], which is an inversion of MIC or MBC in the unit of μM to observe positive trends of system parameters. The subscripts '*c*' and '*a*' stand for cation and anion, respectively. Because experimentally determined LFER descriptors of IL ions are not available, the descriptors were calculated by our previous study [63]. And only experimentally determined LFER descriptors of Na^+ were referred from literature [59]. The calculation methods are given in the section of computational details and the calculated models are provided in supporting information.

2.2. Database of ionic liquids and their abbreviations

For modelling, MIC and MBC values of ILs towards *E. coli*, *S. aureus* and *C. albicans* were collected from literatures [9–12,19,64]. However, the some datasets of some current articles [15–19] were not considered because they used different incubation times for measuring MIC and MBC, and large differences of magnitude were observed between used data and excluded data. Actually, the collected datasets (MIC and MBC) for modelling, which were from Perznak et al. [9,10], Cieniecka-Roslonkiewicz et al. [11], Łuczak et al. [64], and Hou et al. [12], were measured after 24 h incubating time, while Yu et al. [17], Hajfarajollah et al. [19], and Mester et al. [18] measured MIC or MBC for 16 h, 48 h, 30 min–18 h, respectively. The difference of the incubating time may produce large deviation even for the same ILs, which causing severe prediction error for modelling. And it was also observed large data differences of magnitude from Ferraz et al. [16], when comparing with that from Cieniecka-Roslonkiewicz et al. [11]. For example, log MIC value of [P666-14] Cl by Ferraz et al. [16] is 3.40 for both *E. coli* and *S. aureus*, while Cieniecka-Roslonkiewicz et al. [11] presented the values of 1.49 and 1.78, respectively. Also even though direct comparison is not available, log MIC of [IM12] Br to *S. aureus* is 1.70 which has four magnitude difference from that (5.42) of [IM12] Cl from Łuczak et al. [64].

The selected ILs are comprised of 4 head groups (ammonium, phosphonium, imidazolium, pyridinium) with differently functionalized substitutes, as shown in Fig. 1. The studied anions are lactate $[Lac]^-$, histidinate $[His]^-$, aspartate $[Asp]^-$, asparaginate $[Asn]^-$, glutaminate $[Glu]^-$, methioninate $[Met]^-$, serinate $[Ser]^-$, isoleucinate $[Iso]^-$, threoninate $[Thr]^-$, glycinate $[Gly]^-$, leucinate $[Leu]^-$, valinate $[Val]^-$, alaninate $[Ala]^-$, lysinate $[Lys]^-$, argininate $[Arg]^-$, glutamine $[Gln]^-$, proline $[Pro]^-$, phenylanine $[Phe]^-$, tryptophan $[Trp]^-$, tetrafluoroborate $[BF_4]^-$, acetate $[1COO]^-$, decanoate $[9COO]^-$, bis(trifluoromethylsulfonyl) amide $[(CF_3SO_2)_2N]^-$, dicyanide $[N(CN)_2]^-$, hexafluorophosphate $[PF_6]^-$, I^-, Cl^-, Br^-, methylsulphate $[C1SO_4]^-$, p-Toluenesulfonate [4MePhSO3]-, octylsulphate $[C_8SO_4]^-$, trifluoromethansulfonate $[CF_3SO_3]^-$ and nitrate $[NO_3]^-$.

2.3. Computational details

To obtain LFER descriptors, sub-parameters were calculated by using density functional theory (DFT) [65] and conductor-like screening model (COSMO) [66] in the Turbomole program package (version 5.10) [67]. First, (RI-)BP86/SV(P) [58–71] optimizations