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Significant contributions of ionic liquids containing tetrafluoroborate and trifluoromethanesulfonate to antagonisms and synergisms in multi-component mixtures

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ABSTRACT

Recent toxicity studies on ionic liquids (ILs) are challenging their postulation as green solvents. Previous reports on mixtures containing ILs make it urgent to reveal the responsible components for the toxicity interactions. For that purpose, eight ILs, four consisting of 1-ethyl-3-methylimidazolium ([emim]) and the others of 1-butyl-3-methylimidazolium ([bmim]), were selected as mixture components. The concentrations of eight ILs in mixtures were set up by the uniform design. The inhibition toxicities of single ILs and mixtures to *Vibrio qinghaiensis* sp.-Q67 were determined by microplate toxicity analysis. Combined toxicity was evaluated by the difference between the effects observed and predicted by the concentration addition model. Using the variable selection and modeling method based on the prediction (VSMP), it was found that the antagonism/synergism induced by the mixtures of eight ILs was related to [emim]BF_4/[emim]CF_3SO_3. To further illustrate the toxicity interactions, eight ILs were split into two mixture groups, one containing four [emim]-based ILs and the other four [bmim]-based ILs. The [emim]-group exhibited synergism while [bmim]-group resulted in antagonism. It was interesting that both the synergism and antagonism well related to the concentration ratio of ILs with BF_4^-. When ILs with BF_4^- were deleted from corresponding mixtures, the toxicity interactions (synergism/antagonism) disappeared.

1. Introduction

Ionic liquids (ILs) are widely applied in various fields for their special physicochemical properties [1,2]. However, ILs are not always green [3]. Along with their increasing application, it was found that ILs entered into the aquatic environment through wastewater or accidental input to produce possible harmful effects to the ecological system [4]. It have been demonstrated that ILs are toxic to luminescent bacteria, algae, terrestrial plants, earthworm and zebrafish [5–10]. Moreover, toxicity interactions were observed between ILs and heavy metals [8], ILs and pesticides [9], and between different ILs [10]. However, these limited studies neither effectively cover the whole possible concentration space due to their poor experimental design, nor point out the related components with the observed toxicity interactions.

Therefore, the current paper aimed to investigate the toxicity interactions in the mixtures of chosen ILs in the whole concentration regions. The experimental concentrations of ILs in mixtures were set up by the uniform design (UD). The uniformity of experimental region filling of UD guarantees the uniform distribution of various concentrations of all components in the mixtures [11–14]. On the other hand, the experimental efforts of UD are more feasible than the factorial design, especially when the numbers of the components or the concentration levels of the components in the mixtures increase [12,13]. To reveal the related components with the observed toxicity interactions, the variable selection and modeling method based on the prediction (VSMP) was employed [15].

In this paper, eight ILs of two cations, four consisting of 1-ethyl-3-methylimidazolium ([emim]) and the others of 1-butyl-3-methylimidazolium ([bmim]), and six anions were selected as mixture components for their similarities of chemical structures. The microplate toxicity analysis (MTA) [13] was used to determine the inhibition toxicity of single ILs and their mixtures to Q67. The combined toxicity of a mixture was evaluated by the deviation of the effects observed from the effects predicted by the concentration addition (CA) model. The results showed that the antagonism/synergism induced by the mixtures of eight ILs was related to [emim]BF_4/[emim]CF_3SO_3. To further illustrate the toxicity interactions, eight ILs were split into two mixture groups. It

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was found that both the synergism and antagonism well related to the concentration ratio of ILs with BF_4^-.

2. Materials and methods

2.1. Tested ionic liquids

Eight ILs contained two cations, [emim] and [bmim], and six anions. [emim]BF_4 (purity >99%) was purchased from J&K. [emim]CF_3SO_3 (purity >97%), [emim]$C_7H_7SO_3$ (purity >97%), [bmim]BF_4 (purity >97%) and [bmim]CH_3SO_4 (purity >97%) were purchased from Merck. [emim]Cl (purity >97%) was purchased from Acros. [bmim]Br (purity >97%) was purchased from Fluka and [bmim]Cl (purity >99%) was purchased from Lihua Pharmceutical.

2.2. Test organism and cultivation

Vibrio qinghaiensis sp.-Q67 (Q67) was cultured at 22 °C using the same procedure as our previous work [13].

2.3. Toxicity tests

The MTA was used to determine the toxicities of single ILs and mixtures to *V. qinghaiensis* sp.-Q67, and the toxicity effects (E) were expressed as the inhibition ratio [12,13] according to the following formula (Eq. (1)):

$$E = \frac{I_0 - I}{I_0} \times 100\% \quad (1)$$

where I is the average of the relative light unit of Q67 exposed to the test toxicant or mixtures (three parallels for each replicate) and I_0 refers to the average of the relative light unit of Q67 exposed to the controls (12 parallels for each replicate).

2.4. Mixture design

The concentrations of different components in the mixtures were specified using the UD with a series of effective concentrations (EC_x) from toxicity tests on single chemicals as the levels in UD [12–14]. Briefly, the UD tables employed in this paper were $U_{11}(11^{10})$ and $U_7(7^6)$, where the subscript 11 and 7 referred to the number of the mixture experiments and the superscript 10 and 6 to the maximum allowed the number of the factors (ILs) in each experiment (mixture). In this paper, the $U_{11}(11^{10})$ was selected for the mixtures of eight ILs and $U_7(7^6)$ for four ILs.

The uniform design made the experimental points uniformly scattered in the region covering all the possible effects. Each experimental point in UD experiment represented one mixture. Subsequently, each experimental point was diluted to a series of mixtures using the fixed ratio ray design [10] and the series of mixtures construct a concentration–response curve (CRC) of a mixture with a fixed ratio (or a mixture ray). Here, the fixed ratio or concentration ratio (P_i) of a component refers to the ratio of the concentration of the component to the sum of the concentrations of all the components in a mixture. Through this way, the mixtures not only represented all the effective concentrations of each IL, but also can simulate various possible concentration compositions in the environment.

Various EC_x values used in UD experiments can be computed from the fitted CRC function listed in Table 1. Various EC_x and P_i values of every component in the uniform design mixtures were listed in Tables 2 and 3, respectively. To further illustrate the toxicity interactions, eight ILs were split into two groups, one consisting of [emim]-based ILs and the other of [bmim]-based ones.

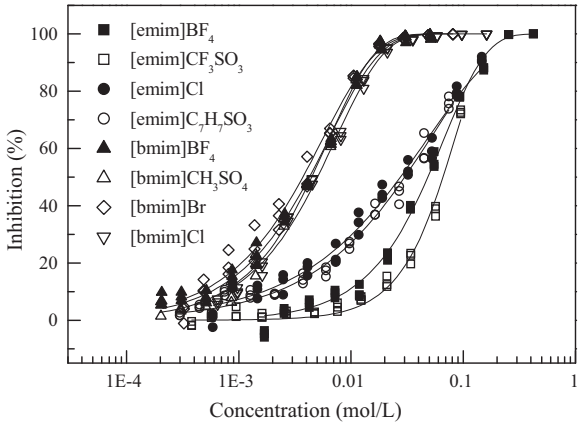

Fig. 1. The concentration–response curves of eight ionic liquids (ILs) to Q67. [emim]: 1-ethyl-3-methylimidazolium; [bmim]: 1-butyl-3-methylimidazolium.

2.5. Evaluation of mixture toxicity interaction

Different types of toxicity interactions, including antagonism and synergism, were evaluated by the comparison of the effects observed to the effects predicted by the CA model [16]. The experimental concentration inhibition ratio data were fitted to the Logit (Eq. (2)) or Weibull functions (Eq. (3)) [17]. The fitted function with higher correlation coefficient (R) or lower root mean square error ($RMSE$) was used to calculate the observed effects of single ILs or mixtures. The formulas of the Logit and Weibull functions were written as follows:

$$E = \frac{1}{1 + \exp(-\alpha - \beta \log_{10}(c))} \quad (2)$$

$$E = 1 - \exp(-\exp(\alpha + \beta \log_{10}(c))) \quad (3)$$

where α (the location parameter) and β (slope parameter) are the parameters to be estimated; c is the concentration of single ILs or the mixture.

To quantitate and visualize the toxicity interaction in the effect range of 0–100%, a deviation of the observed effects from the predicted effects was treated as Y-axis, while the predicted effect was treated as X-axis. The more the deviation in a certain effect (E) is, the more obvious the toxicity interaction is.

2.6. Relation the interaction with ratio of a component

The VSMP procedure was related the toxicity interaction to the concentration ratio of some a component [15]. The interaction was expressed as a deviation of the effect observed from the effects predicted by the CA model. When the deviation is positive/negative, the interaction produces synergism/antagonism. A good relationship between the deviation and the ratio of a component implies that the component plays an important role in the interaction.

3. Results

3.1. Toxicities of single ionic liquids

The concentration–response (inhibition ratio) curves (CRCs) of eight single ILs to Q67 were all effectively described by the Weibull function (Table 1). The CRCs fitted by the Weibull function were shown in Fig. 1 together with the experimental concentration-inhibition ratio points. From Table 1, the values of $RMSE$ of <0.0311 and R of >0.993) revealed a good relationship between the exposed concentrations of single ILs and their inhibition ratios. Various EC_x, e.g. EC_{50}, were calculated from the fitted function with α and

Table 1
The fitted concentration–response functions, statistics (the correlation coefficient, *R*, and root mean square error, *RMSE*), and EC_{50} values (with 95% confidence intervals) of eight ILs.

IL	Function [a]	α	β	*R*	*RMSE*	EC_{50} (mol/L)
[emim]BF_4	Weibull	3.05	2.60	0.997	0.0265	4.85E−02 (3.92E−02, 6.10E−02)
[emim]CF_3SO_3	Weibull	3.79	3.52	0.996	0.0211	6.59E−02 (5.72E−02, 7.80E−02)
[emim]Cl	Weibull	2.04	1.54	0.993	0.0311	2.74E−02 (1.69E−02, 4.45E−02)
[emim]$C_7H_7SO_3$	Weibull	2.14	1.65	0.995	0.0220	3.03E−02 (2.19E−02, 4.27E−02)
[bmim]BF_4	Weibull	4.73	2.15	0.998	0.0186	4.26E−03 (3.44E−03, 5.42E−03)
[bmim]CH_3SO_4	Weibull	5.30	2.41	0.999	0.0156	4.45E−03 (3.74E−03, 5.42E−03)
[bmim]Br	Weibull	4.69	2.08	0.998	0.0221	3.71E−03 (2.69E−03, 5.18E−03)
[bmim]Cl	Weibull	4.90	2.29	0.998	0.0189	5.01E−03 (4.20E−03, 6.18E−03)

β. From the results in Table 1 and Fig. 1, the toxicity effects of the ILs with [bmim] were generally more serious than those with [emim]. For the ILs with [emim], the order of the toxicity (EC_{50}) was [emim]Cl > [emim]$C_7H_7SO_3$ > [emim]BF_4 > [emim]CF_3SO_3. For the ILs with [bmim], the order was [bmim]Br > [bmim]BF_4 > [bmim]CH_3SO_4 > [bmim]Cl.

3.2. The interaction analysis of the mixtures of eight ILs

The EC_x and concentration ratios of various IL components in the mixtures of eight ILs (noted UT group) were shown in Tables 2 and 3, respectively. The observed CRCs were also fitted by Logit or Weibull function, and the model parameters, some statistics and EC_{50} values were listed in Table 4. The values of *RMSE* (<0.0504) and *R* (>0.986) as in Table 4 could describe the well fitted relationships between the exposed total concentrations of ILs and the inhibition ratios. The toxicity interaction profile (plot of $E_{OBS} - E_{CA}$ versus E_{CA}) of 11 mixture rays was shown in Fig. 2A.

Although almost all of the curves showed deviations from the predictive values (see Fig. 2A), the curves of UT7, UT8 and UT10 displayed obvious synergisms. Meanwhile, UT2 and UT11 exhibited obvious antagonisms at a high concentration region. The VSMP results (Table 5) showed a good relationship between the deviation and the concentration ratio of [emim]BF_4 or [emim]CF_3SO_3 in the UT group, which implies the ILs plays an important rules in mixture toxicity interaction. Meanwhile, the negative correlations to [emim]BF_4 demonstrated its relationship to the antagonism of the mixtures and the positive correlations to [emim]CF_3SO_3 demonstrated its relationship to the synergism.

3.3. The interaction analysis of the mixtures of four ILs

As above shown, both [emim]BF_4 and [emim]CF_3SO_3 had the same cation of [emim], which reminded us to think whether the ILs containing the cation of [bmim] can contribute to the toxicity interactions or not. Thus, the UT group was split into two

Table 2
Various effective concentrations (EC_x) of eight ILs in the mixtures designed by the uniform design procedure.

Mixture ray [a]	[emim]BF_4	[emim]CF_3SO_3	[emim]Cl	[emim]$C_7H_7SO_3$	[bmim]BF_4	[bmim]CH_3SO_4	[bmim]Br	[bmim]Cl
UT1	EC_{50}	EC_5	EC_{15}	EC_{25}	EC_{10}	EC_{20}	EC_{30}	EC_{35}
UT2	EC_{45}	EC_{10}	EC_{30}	EC_{50}	EC_{20}	EC_{40}	EC_5	EC_{15}
UT3	EC_{40}	EC_{15}	EC_{45}	EC_{20}	EC_{30}	EC_5	EC_{35}	EC_{50}
UT4	EC_{35}	EC_{20}	EC_5	EC_{45}	EC_{40}	EC_{25}	EC_{10}	EC_{30}
UT5	EC_{30}	EC_{25}	EC_{20}	EC_{15}	EC_{50}	EC_{45}	EC_{40}	EC_{10}
UT6	EC_{25}	EC_{30}	EC_{35}	EC_{40}	EC_5	EC_{10}	EC_{15}	EC_{45}
UT7	EC_{20}	EC_{35}	EC_{50}	EC_{10}	EC_{15}	EC_{30}	EC_{45}	EC_{25}
UT8	EC_{15}	EC_{40}	EC_{10}	EC_{35}	EC_{25}	EC_{50}	EC_{20}	EC_5
UT9	EC_{10}	EC_{45}	EC_{25}	EC_5	EC_{35}	EC_{15}	EC_{50}	EC_{40}
UT10	EC_5	EC_{50}	EC_{40}	EC_{30}	EC_{45}	EC_{35}	EC_{25}	EC_{20}
UT11	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
UB1	–	–	–	–	EC_{10}	EC_{20}	EC_{30}	EC_{35}
UB2	–	–	–	–	EC_{20}	EC_{40}	EC_5	EC_{15}
UB3	–	–	–	–	EC_{30}	EC_5	EC_{35}	EC_{50}
UB4	–	–	–	–	EC_{40}	EC_{25}	EC_{10}	EC_{30}
UB5	–	–	–	–	EC_{50}	EC_{45}	EC_{40}	EC_{10}
UB7	–	–	–	–	EC_{15}	EC_{30}	EC_{45}	EC_{25}
UB8	–	–	–	–	EC_{25}	EC_{50}	EC_{20}	EC_5
UB9	–	–	–	–	EC_{35}	EC_{15}	EC_{50}	EC_{40}
UB10	–	–	–	–	EC_{45}	EC_{35}	EC_{25}	EC_{20}
UB11	–	–	–	–	EC_{50}	EC_{50}	EC_{50}	EC_{50}
UB4′	–	–	–	–	–	EC_{25}	EC_{10}	EC_{30}
UB5′	–	–	–	–	–	EC_{45}	EC_{40}	EC_{10}
UB10′	–	–	–	–	–	EC_{35}	EC_{25}	EC_{20}
UE1	EC_{50}	EC_5	EC_{10}	EC_{20}	–	–	–	–
UE2	EC_{40}	EC_{10}	EC_{30}	EC_{50}	–	–	–	–
UE3	EC_{30}	EC_{20}	EC_{50}	EC_{10}	–	–	–	–
UE4	EC_{20}	EC_{30}	EC_5	EC_{40}	–	–	–	–
UE5	EC_{10}	EC_{40}	EC_{20}	EC_{50}	–	–	–	–
UE6	EC_5	EC_{50}	EC_{40}	EC_{30}	–	–	–	–
UE7	EC_{50}	EC_{50}	EC_{50}	EC_{50}	–	–	–	–
UE1′	–	EC_5	EC_{10}	EC_{20}	–	–	–	–
UE2′	–	EC_{10}	EC_{30}	EC_{50}	–	–	–	–

[a] UT group refers to the uniform design mixture of total eight ILs, UE group to the uniform design mixture of four [emim]-based IL, and UB to the uniform design mixture of four [bmim]-based ILs.

Table 3
The concentration ratios (P_i) of various ILs in the mixture rays computed from Table 2.[a]

Mixture ray	$P_{[emim]BF_4}$	$P_{[emim]CF_3SO_3}$	$P_{[emim]Cl}$	$P_{[emim]C_7H_7SO_3}$	$P_{[bmim]BF_4}$	$P_{[bmim]CH_3SO_4}$	$P_{[bmim]Br}$	$P_{[bmim]Cl}$
UT1	0.248	0.273	0.0470	0.256	0.0240	0.0640	0.0480	0.0420
UT2	0.115	0.231	0.0790	0.461	0.0280	0.0750	0.00300	0.00800
UT3	0.125	0.387	0.217	0.119	0.0580	0.0100	0.0390	0.0450
UT4	0.0870	0.386	0.00400	0.383	0.0700	0.0440	0.00700	0.0190
UT5	0.0860	0.529	0.0470	0.0720	0.112	0.103	0.0440	0.00600
UT6	0.0570	0.493	0.101	0.288	0.00600	0.0160	0.0100	0.0290
UT7	0.0470	0.576	0.213	0.0330	0.0200	0.0530	0.0440	0.0150
UT8	0.0330	0.596	0.0120	0.217	0.0340	0.0920	0.0140	0.00200
UT9	0.0250	0.739	0.0590	0.0120	0.0580	0.0260	0.0540	0.0270
UT10	0.0100	0.611	0.104	0.140	0.0620	0.0490	0.0150	0.00900
UT11	0.256	0.348	0.145	0.159	0.0220	0.0230	0.0200	0.0270
UB1					0.134	0.362	0.268	0.235
UB2					0.246	0.656	0.0260	0.0720
UB3					0.384	0.0680	0.255	0.293
UB4					0.501	0.317	0.0480	0.133
UB5					0.422	0.388	0.166	0.0240
UB7					0.151	0.402	0.336	0.111
UB8					0.238	0.649	0.0960	0.0170
UB9					0.355	0.156	0.327	0.163
UB10					0.460	0.363	0.112	0.065
UB11					0.335	0.355	0.185	0.125
UB4′					–	0.387	0.0930	0.520
UB5′					–	0.531	0.364	0.104
UB10′					–	0.484	0.240	0.276
UE1	0.710	0.175	0.0240	0.0900				
UE2	0.383	0.199	0.106	0.312				
UE3	0.306	0.357	0.313	0.0250				
UE4	0.220	0.529	0.00700	0.244				
UE5	0.0930	0.550	0.0510	0.306				
UE6	0.0480	0.659	0.174	0.119				
UE1′	–	0.605	0.0830	0.312				
UE2′	–	0.322	0.171	0.506				

[a] The concentration ratio of a component, *P*, refers to the ratio of the concentration of the component to the sum of the concentrations of all the components in a mixture.

Table 4
The fitted concentration–response functions, statistics (the correlation coefficient, *R*, and root mean square error, *RMSE*), and EC_{50} values (with 95% confidence intervals) of 33 IL mixture rays.

Mixture ray	Function[a]	α	β	*R*	*RMSE*	EC_{50} (mol/L)
UT1	Weibull	2.40	1.94	0.994	0.0355	3.75E−02 (2.58E−02, 5.49E−02)
UT2	Weibull	1.89	1.72	0.991	0.0326	4.88E−02 (3.28E−02, 7.29E−02)
UT3	Weibull	1.92	1.55	0.996	0.0230	3.35E−02 (2.43E−02, 4.73E−02)
UT4	Weibull	1.57	1.29	0.997	0.0167	3.15E−02 (2.34E−02, 4.31E−02)
UT5	Weibull	2.13	1.56	0.986	0.0484	2.51E−02 (1.32E−02, 4.65E−02)
UT6	Logit	3.49	2.15	0.994	0.0299	2.38E−02 (1.61E−02, 3.73E−02)
UT7	Logit	4.70	2.27	0.997	0.0236	8.50E−03 (6.27E−03, 1.22E−02)
UT8	Logit	6.28	2.89	0.993	0.0429	6.71E−03 (4.39E−03, 1.10E−02)
UT9	Weibull	3.06	1.81	0.998	0.0212	1.28E−02 (9.84E−03, 1.72E−02)
UT10	Logit	5.73	2.94	0.998	0.0205	1.13E−02 (8.88E−03, 1.53E−02)
UT11	Weibull	1.80	1.49	0.994	0.0272	3.52E−02 (2.20E−02, 5.75E−02)
UB1	Logit	7.20	3.16	0.999	0.0159	5.27E−03 (4.52E−03, 6.53E−03)
UB2	Logit	5.90	2.63	0.999	0.0115	5.71E−03 (4.56E−03, 7.85E−03)
UB3	Logit	5.82	2.56	0.999	0.0180	5.39E−03 (3.93E−03, 7.70E−03)
UB4	Logit	4.71	2.20	0.998	0.0194	7.23E−03 (5.56E−03, 1.01E−02)
UB5	Logit	4.98	2.26	0.999	0.0129	6.26E−03 (5.04E−03, 8.29E−03)
UB7	Logit	7.29	3.17	0.999	0.0111	5.02E−03 (4.31E−03, 6.19E−03)
UB8	Logit	6.17	2.74	0.998	0.0190	5.50E−03 (4.57E−03, 7.45E−03)
UB9	Weibull	3.89	1.95	0.996	0.0338	6.56E−03 (4.54E−03, 9.78E−03)
UB10	Weibull	2.29	1.29	0.997	0.0201	8.72E−03 (5.72E−03, 1.36E−02)
UB4′	Weibull	5.08	2.26	0.999	0.0131	3.89E−03 (3.55E−03, 4.55E−03)
UB5′	Weibull	4.35	1.91	0.998	0.0191	3.39E−03 (2.87E−03, 4.18E−03)
UB10′	Weibull	4.60	2.11	0.999	0.0152	4.49E−03 (3.81E−03, 5.22E−03)
UE1	Weibull	1.70	1.15	0.993	0.0355	1.60E−02 (8.74E−03, 3.02E−02)
UE2	Weibull	2.01	1.26	0.993	0.0358	1.30E−02 (7.38E−03, 2.36E−02)
UE3	Weibull	2.60	1.98	0.988	0.0504	3.18E−02 (1.83E−02, 5.53E−02)
UE4	Weibull	2.26	1.82	0.987	0.0421	3.61E−02 (2.18E−02, 5.89E−02)
UE5	Logit	2.19	1.72	0.988	0.0339	5.33E−02 (2.89E−02, 8.22E−02)
UE6	Weibull	1.56	1.36	0.994	0.0261	3.83E−02 (2.33E−02, 6.63E−02)
UE7	Logit	3.04	1.91	0.990	0.0368	2.56E−02 (1.48E−02, 4.70E−02)
UE1′	Weibull	2.94	2.44	0.994	0.0268	4.41E−02 (3.24E−02, 6.46E−02)
UE2′	Weibull	2.76	2.23	0.996	0.0205	3.96E−02 (3.00E−02, 5.64E−02)

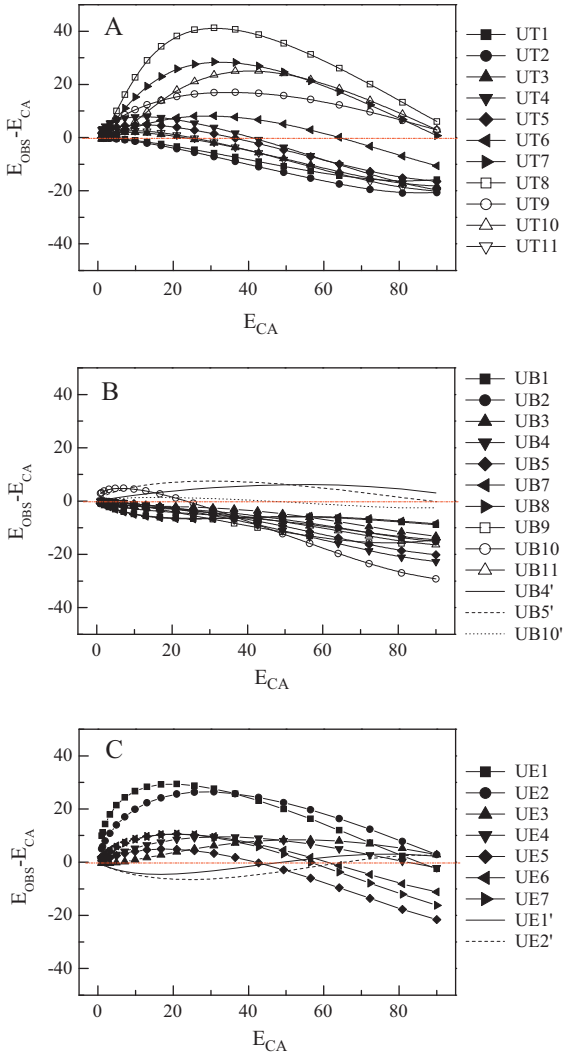

Fig. 2. Plot of the deviation of the effects observed from those predicted by the concentration addition (CA) model versus the predictive effects. UT: the uniform design mixture of total eight ILs, UE: the uniform design mixture of four [emim]-based ILs, UB: the uniform design mixture of four [bmim]-based ILs.

subgroups, one consisting of [bmim]-based ILs (noted as UB group) and the other of [emim]-based ILs (UE group) to further illustrate the toxicity interactions.

It should be indicated that 10 mixture rays in UB group came from those in UT group where the EC_x of four ILs were the same as EC_x of the corresponding components in UT group. The other ray, UT6, was not investigated further in the UB group because there was no toxicity interactions observed. In the UB group, the UB4, UB5 and UB10 showed obvious antagonisms at high concentration regions as shown in Fig. 2B. The VSMP result revealed that [bmim]BF_4 was a relative component playing an important role in the mixtures. The negative correlation to [bmim]BF_4 demonstrated the antagonism. To testify it, [bmim]BF_4 was deleted from UB group to form three new ternary mixtures (UB4′, UB5′ and UB10′ in Table 2) and it was shown that there were no obvious interactions in the ternary mixtures (shown in Fig. 2B). Therefore, the occurrence and disappearance of the antagonisms were closely related to the presence and absence of [bmim]BF_4 in the UB group.

To examine the toxicity interaction of the mixtures without [bmim]-based ILs, we also designed a UE group using another uniform table, $U_7(7^6)$ and various EC_x and P_i values were listed in Tables 2 and 3. Obvious synergisms were observed in UE1 and UE2 (Fig. 2C). The VSMP result showed that [emim]BF_4 played an important role in the interaction of UE group (Table 5). The positive correlation to [emim]BF_4 showed a synergism. In the same way as UB group, [emim]BF_4 was deleted from the UE mixtures to construct two new ternary mixtures (UE1′ and UE2′) and it was shown that there are no interaction in the ternary mixtures (Fig. 2C). Therefore, the occurrence and disappearance of the synergisms were closely related to the presence and absence of [emim]BF_4 in the UE group.

Table 5
The synergism/antagonism expressed by the deviation of the effect observed from one predicted by the concentration addition model being positively/negatively related to the concentration ratio of some component in the mixture.

Component	n[a]	r[b]	Toxicity interaction
[emim]BF_4 in UT group	11	−0.575	Antagonism
[emim]CF_3SO_3 in UT group	11	+0.677	Synergism
[bmim]BF_4 in UB group	10	−0.687	Antagonism
[emim]BF_4 in UE group	6	+0.737	Synergism

[a] n refers to the sample number;
[b] r refers to the correlation coefficient between the deviations and the ratios of some a component (IL).

4. Discussion

4.1. Toxicities of single ILs

The more toxic effects of the [bmim]-based ILs than [emim]-based ones were in accordance with previous reports [18]. The [emim] or [bmim] ILs with different anions showed no significant difference in toxic effects, i.e., their toxicities did not simply increase or decrease with the change of the structure of the anions. Despite of the non-obvious influences of inorganic anions on the toxicities of single ILs [19,20], their influences on the toxicity interaction of mixtures might not be neglected.

4.2. Related component to the toxicity interaction

When the mixtures of eight ILs changed into the ones of four [emim]- or [bmim]-based ILs, three alterations happened: (1) the correlation of [emim]CF_3SO_3 to the synergisms became less significant ($r < 0.575$); (2) the roles of [emim]BF_4 changed into contributing to the synergisms from contributing to the antagonisms; (3) the contributions of [bmim]BF_4 to the antagonisms emerged. In the mixtures producing toxicity interactions, the concentration ratios of the related components such as [emim]CF_3SO_3, [emim]BF_4 and [bmim]BF_4 also changed obviously (Table 3). For example, the concentration ratios of [emim]CF_3SO_3 in UT group changed from 0.231 in UT2 to 0.739 in UT9.

However, it is well known that the toxicity interaction occurs between two or among many components, and it is impossible to be decided only by one component in the multi-component mixtures. Moreover, the contributions of each individual chemical to the total toxicities of the mixtures may differ substantially [21]. Thus, the interactions induced by some a component in different mixtures were probably not the same. For example, [emim]BF_4 resulted in an antagonism in UT group while produced a synergism in UE group. This was also supported by previously reported interactions between ILs and insecticides where the interaction altered from addition to antagonism [22].

5. Conclusion

The toxicities of [emim]-based ILs were lower than those of [bmim]-based ILs. The synergism/antagonism related to [emim]CF_3SO_3/[emim]BF_4 in UT group of eight ILs. The synergism

in UE group related to [emim]BF_4 while the antagonism in UB group related to [bmim]BF_4 in the mixtures of four ILs. When [emim]BF_4/[bmim]BF_4 was deleted from the UE/UB group, the synergism/antagonism disappeared.

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