



Molecular docking research for the extraction of typical natural products by imidazolium-based ionic liquids

Pengfei Chen, Yu Cao, Tian Yao, Lu Zhou, Shun Yao and Hang Song*

School of Chemical Engineering, Sichuan University, Chengdu, China

ABSTRACT

The experimental information of imidazolium-based ionic liquids in the extraction of natural products from literatures was firstly collected to summarize the extraction rules of natural products in ionic liquids. The structures of ionic liquid, water and natural products were optimized by Gaussian03 to obtain the optimal conformation. Then AutoDock 4.0 was employed to calculate the intermolecular interactions between the ILs and the natural products, and the docking simulation results and the experimental data were compared. The specific interaction energy between gallic acid and ionic liquid 1-butyl-3-methylimidazolium octylsulfate ($[C_4mim][C_8H_{17}SO_4]$) was analyzed to further investigate the extraction mechanism. The results demonstrated that the higher absolute value of binding free energy was, the easier natural products could be extracted by ionic liquid. This study was expected to provide a new method for fast selecting specific ionic liquid in the extraction of target natural products.

Keywords: ionic liquid, imidazolium-based, natural products, extraction, docking

INTRODUCTION

Liquid-liquid extraction has often been a favored choice for the separation of the natural products. Traditional natural products extraction [1-3], however, often employs an organic solvent selected through industrious experiments and an aqueous solution as the two immiscible phases, which often led to serious emulsification in some cases [4]. Moreover, the increasing emphasis on the adoption of environmentally benign technologies may make current processes seem increasingly anachronistic because of high usage of toxic, flammable, volatile organic solvent. Therefore, it is desired to develop some safe and environmentally benign extraction solvents.

Ionic liquids (ILs) have aroused increasing interest for their promising role as alternative media in separation [5, 6]. They can dissolve a wide range of organic and inorganic compounds [7, 8]. Also, they have negligible vapor pressure and are relatively thermal stable, which can avoid environmental and safety problems due to the usage of conventional organic solvents. Therefore, they are expected to be novel liquid-liquid extraction solvents to replace those traditional solvents. Recently, ILs have more and more been used in separation and purification of natural products with its unique advantage. For instance, Yu et al. reported that 1-methyl-3-butyl-imidazolium hexafluorophosphate ($[BMIM][PF_6]$) could be used as extraction solvent for separation ferulic acid and caffeic acid [9]. It also demonstrated that ILs can be recycled, which could reduce harm to environment and operators. In another study, the gallic acid was been successfully extracted by 1-butyl-3-methylimidazolium methylsulfate ($[BMIM][CH_3SO_4]$)-H₂O solution with relatively high extraction rate of 52.81% [10].

Although ILs are applied in extracting various natural products, few related extraction mechanisms have been explored, especially for the selecting specific ILs in the extraction of natural products. In this study, based on the experimental information of imidazolium-based ILs extracting natural products from literatures, molecular docking was firstly explored to investigate the extraction mechanism, which also provided a kind of new method of fast selecting specific ILs for exacting target natural products.

EXPERIMENTAL SECTION

Preparation of the experimental data

Considering imidazolium-based ILs had been currently widely used in extracting natural products, the extraction data collected from the literatures were all about this type. Ten typical groups (Table 1) were selected to investigate the relationship between the structure and extraction yield, which involved six kinds of natural products containing aromatic ring and six imidazolium-based ILs. Their structures are shown in Fig.1.

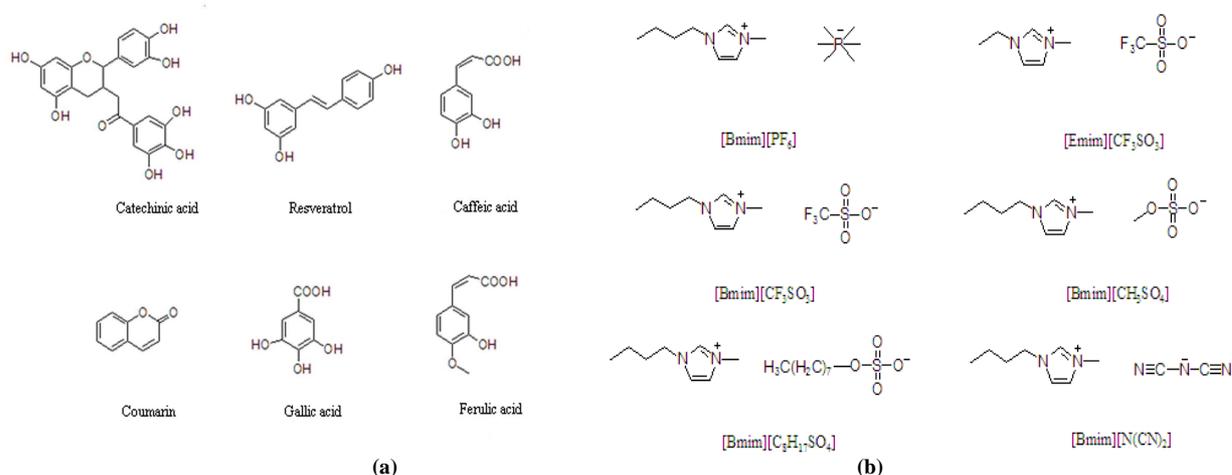


Fig 1 The structures of natural products (a) and ionic liquids (b)

Table 1 The experimental data of ionic liquids extracting natural products

Entry	Natural products	Solvent of Source	Ionic liquid	Yield /%	Ref.
1	catechinic acid	H ₂ O + wine substrate	[Bmim][PF ₆]	98.9	[11]
2	resveratrol	standard solution + wine substrate	[Bmim][PF ₆]	98.1%	[11]
3	caffeic acid	H ₂ O	[Bmim][PF ₆]	45.7%	[9]
4	ferulic acid	H ₂ O	[Bmim][PF ₆]	91.9%	[9]
5	coumarin	H ₂ O	[Bmim][PF ₆]	94.55%	[12]
6	gallic acid	Na ₂ SO ₄ solution	[Emim][CF ₃ SO ₃] ^a	14.7%	[10]
7	gallic acid	Na ₂ SO ₄ solution	[Bmim][CF ₃ SO ₃] ^b	34.66%	[10]
8	gallic acid	Na ₂ SO ₄ solution	[Bmim][CH ₃ SO ₄]	52.81%	[10]
9	gallic acid	Na ₂ SO ₄ solution	[Bmim][C ₈ H ₁₇ SO ₄]	18.53%	[10]
10	gallic acid	Na ₂ SO ₄ solution	[Bmim][N(CN) ₂] ^c	26.02%	[10]

a: 1-ethyl-3-methylimidazolium trifluoromethanesulfonate;

b: 1-butyl-3-methylimidazolium methylsulfate

c: 1-butyl-3-methylimidazolium dicyanamide

Optimization of the molecular structure

The 3D structural coordinates of the RTILs and the natural products were obtained from the Cambridge Structural Database (CSD) [13]. In order to get the preferential conformation as the molecular structure for docking, Gaussian03 (revision C.02, Gaussian, Inc., Wallingford, CT) was employed to optimize the molecular structure.

Docking simulation

In this study, AutoDock 4.0 (freely available at <http://www.autodock.scripps.edu/>) was employed to calculate the intermolecular interactions between the ILs and the natural products. AutoDock performed the docking of the analytes to a set of grids which are used to describe the natural products and AutoGrid precalculates these grids. The grid box was all the same for the ILs and the center of grid box was fixed on macromolecular, so the space was the same for the natural products. And the grid box was enlarged until the lowest binding free energy was achieved. In the LGA calculation, the parameters in AutoDock began with 'ga' (genetic algorithm) [14]. In this study, the number of ga_run was set in 100 considering a few rotational bonds. The ga_num_evals was set in long (2.5e⁷) and the ga_pop_size was set in 300 [15]. All above docking conditions were the same for all of the ILs to make the results comparable. The results from the docking were evaluated according to their energy scores, which were adopted by most references [16-18]. At the same time, the solvent molecules from raffinate phase were also docked with the natural products.

RESULTS AND DISCUSSION

Preferential conformation of the ILs and natural products

Preferential conformation of the ILs and natural products (see Fig.2) was achieved by the density functional theory (DFT) method and DFT calculations were performed at the B3LYP^{[19, 20)]/6-31G(d)} level of theory using Gaussian 03 software.

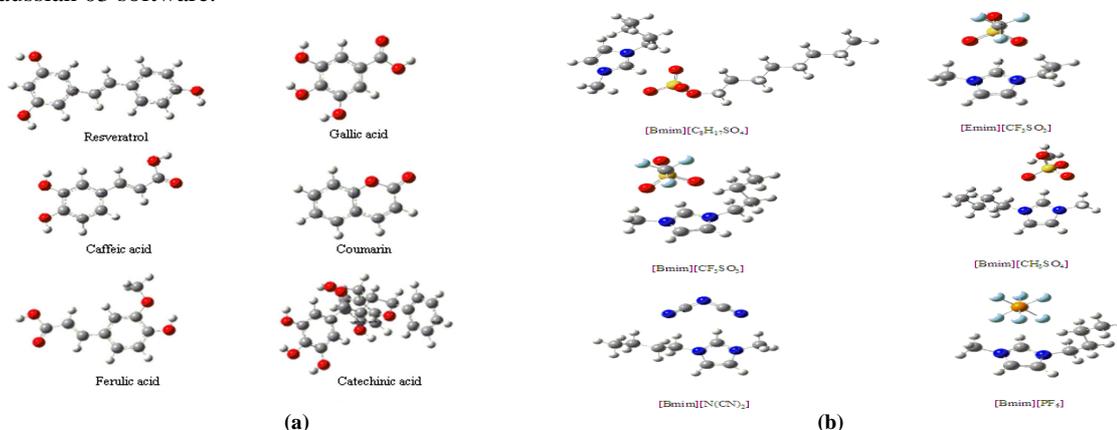


Fig 2 The privileged structures of natural products (a) and ionic liquids (b)

Docking results

The binding free energies in Table 2 between ILs and natural products were all negative, which indicated that the selected ILs were inclined to combining with natural products. Compared to the same ILs used to extract the natural products, it was found that the absolute value of the binding free energy increased as the extraction yield increased, which was in the order of catechin resveratrol >> coumarin > ferulic acid > caffeic acid. Therefore, the binding free energy of ILs could reflect the extraction ability. The higher the absolute value of binding free energy was, the more easily natural products could be extracted by ILs. It provided a method of fast screening specific ILs for exacting natural products.

Table-2 The binding free energy of docking

Entry	Natural products	H ₂ O $\Delta G_w / (\text{kcal.mol}^{-1})$	ILs $\Delta G_{IL} / (\text{kcal.mol}^{-1})$	Extraction rate/%
1	catechinic acid	-1.41	-2.80	98.9
2	resveratrol	-2.08	-2.10	98.1
3	caffeic acid	-1.76	-1.22	45.7
4	ferulic acid	-1.62	-1.35	91.9
5	coumarin	-1.47	-1.85	94.55
6	gallic acid	-1.57	-1.72	14.7
7	gallic acid	-1.57	-1.87	34.66
8	gallic acid	-1.57	-1.80	52.81
9	gallic acid	-1.57	-2.33	18.53
10	gallic acid	-1.57	-1.56	26.02

While the different ILs were used to extract gallic acid, it was unable to achieve the consistency between binding free energy and extraction yield, which could result from small energy gap between different kinds of ionic liquids in the docking. However, compared [Bmim][CF₃SO₃] with [Emim][CF₃SO₃], as the two ILs with same anion and different carbon chain length on cation, it conformed to the rule that the higher the absolute value of binding free energy is, the easier natural products can be extracted by ILs.

Detailed analysis of binding free energy

There were seven groups of data in Table 2 that demonstrated the binding free energy between ILs and natural products was greater than that between water and natural products; in other words, most of the selected ILs have stronger binding affinity than water. However, not all the groups had high extraction capability. So, in order to further investigate the extraction mechanism, the detailed analysis of binding free energy was illustrated by taking the ninth group as an example.

In AutoDock output files, the binding free energy (G_{binding}) was divided into seven parts: vanderwaals energy (G_{vdw}), electrostatic energy (G_{elec}), hydrogen bonding energy (G_{Hbond}), desolvation energy (G_{sol}), torsional free energy (G_{tor}), final total internal energy (G_{final}) and unbond system energy (G_{unbond}). For convenience, the total of G_{vdw} , G_{Hbond} and

G_{sol} in this text was expressed by $G_{\text{vdw+Hbond+sol}}$. The binding free energy can be expressed as follows:

$$G_{\text{binding}} = G_{\text{vdw+Hbond+sol}} + G_{\text{elec}} + G_{\text{final}} + G_{\text{tor}} - G_{\text{unbond}}$$

In the seven energies, the difference of G_{final} of ILs and H_2O was 0.93 kcal/mol, which could directly lead to the energy reduction in the process of combination ILs with gallic acid. The biggest difference of binding free energy was attributed to the $G_{\text{vdw+Hbond+sol}}$ and G_{tor} . Table 3 showed that $G_{\text{vdw+Hbond+sol}}$ was the key factor for the G_{binding} of ILs significantly lower than H_2O . Obviously, the G_{vdw} of ILs was higher than H_2O due to higher molecular weight. Considering the G_{vdw} and G_{sol} had the relatively smaller impact on G_{binding} , G_{Hbond} was investigated. In the calculation result, ILs formed two H-bond with the gallic acid when they were combined in the form of the lowest energy conformation (see Fig. 3). By contrast, there was no H-bond formed in the lowest energy conformation of combination H_2O with gallic acid. However, H-bond was formed in the other energy conformation. It indicated that H-bond played a key role of inducing the difference of $G_{\text{vdw+Hbond+sol}}$.

Moreover, G_{tor} of this IL was 1.57 kcal/mol. It indicated the energy was increased due to the rotation of related bonds in the process of combination, which decreased the molecular affinity between the IL and gallic acid.

Table 3 Comparison of interaction energy between natural products with ionic liquid and H_2O , respectively

Binding free energy type	[Bmim][C ₈ H ₁₇ SO ₄] $\Delta G_{\text{IL}} / (\text{kcal.mol}^{-1})$	H_2O $\Delta G_{\text{w}} / (\text{kcal.mol}^{-1})$
$\Delta G_{\text{vdw+Hbond+sol}}$	-2.45	-1.31
ΔG_{elec}	-0.32	-0.26
ΔG_{final}	-0.93	0.00
G_{tor}	1.57	0.00
ΔG_{unbond}	0.00	0.00
$\Delta G_{\text{binding}}$	-2.33	-1.57

CONCLUSION

In this study, a simple method was developed to fast select specific ionic liquid in the extraction of natural products and it was convenient to common researchers for experiments. Ten groups of imidazolium-based ionic liquids extracting natural products from literature were firstly selected and docked by AutoDock software. It is found that the higher the absolute value of binding free energy is, the more easily natural products can be extracted by ILs. An elaborative analysis of the interaction energy between natural product with ionic liquid and H_2O , respectively, could provide more detailed mechanism of extraction of natural products. Despite all this, further study is still needed to fully understand the extraction mechanism.

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