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Quantum Chemistry Calculation Aided Design of Chiral Ionic Liquid-Based Extraction System for Amlodipine Separation

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Abstract: Amlodipine is a widely used medication in treating hypertension, which is also known as a chiral compound. So far efforts have been made to obtain optically pure (*S*)-amlodipine because (*R*)-amlodipine has poor efficacy and is related to undesirable side effects. However, the available separation methods for amlodipine are still unsatisfactory. Recently, chiral separation has become a promising application of chiral ionic liquids (CILs), because the structural designability enables them adjustable separation efficiency for specific tasks. In this work, a high-efficient CIL-based liquid-liquid extraction system was developed for racemic amlodipine separation with the assistance of quantum chemistry calculations. Enantioselectivity up to 1.35 achieved by the novel system at 298.15 K is significantly higher than other available extraction systems. Moreover, the recycling of CIL can be easily realized by backward extraction of amlodipine, which is important for the industrial application of CILs.

Keywords: ionic liquids, amlodipine, chiral separation, extraction, computational chemistry

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Amlodipine is a third-generation dihydropyridine calcium channel antagonist, which has been widely used for the treatment of cardiovascular diseases such as hypertension and angina pectoris in clinical trials.[1] Known as a chiral compound (Figure 1), its two enantiomers exhibit different biological and pharmacological responses in internal environment. According to the present research, the hypotensive activity mainly arises from (*S*)-amlodipine, which can inhibit the calcium influx across cell membranes.[2] (*R*)-amlodipine has very poor potency, while it may release nitric oxide into the peripheral blood vessels, further resulting in peripheral edema and some other undesirable side effects.[3] It's widely accepted that to isolate (*S*)-amlodipine from its racemate and administer amlodipine in the single enantiomeric form is beneficial for both safety and efficacy of the medication.

The separation of chiral compounds is of substantial significance especially in pharmaceutical industry, which is nevertheless a challenging task due to the fact that enantiomers possess identical physical and chemical properties in achiral environment.[4, 5] Till now, numerous attempts have been made to develop enantioselective separation process to obtain optically pure (*S*)-amlodipine with emphasis on diverse chromatographic techniques,[6, 7] crystallization[8, 9] and extraction.[10, 11] While the chromatographic techniques are only applicable in laboratory scale considering the low capacity and large consumption of solvents.[12] Preferential crystallization featuring the formation of diastereomeric salts using tartaric acid derivatives is the most popular technique in industrial separations. But the disadvantage comes from the extensive use of hazardous organic solvents like DMSO, DMF and DCM, and it just gives rise to the safety and environmental concerns of the industrial

separation process. Furthermore, involved in bulk solid-handling operations, the crystallization separation processes are generally tedious and time-consuming.[13] Liquid-liquid extraction is seen as an alternative technology to overcome the deficiencies of chromatography and crystallization, while the currently available extraction systems comprising conventional chiral extractants are still subjected to poor efficiency and all require to be handled at quite frigid temperature, which means intensive energy consumption. Without doubt, there is a great demand to develop high-efficient and environmentally benign separation process for amlodipine racemate.

Chiral ionic liquids (CILs) are a subclass of ionic liquids, in which the cation, anion or seldom both may be chiral. CILs are of importance due to the unique chiral recognition capability they exhibit,[14, 15] besides other glaring merits inherited from ionic liquids such as low volatility, good chemical stability and excellent solubility.[16] Moreover, CILs are proposed as designable chiral media, because their properties can be finely tuned by modifying the type and composition of the ion pairs for different tasks to increase the separation efficiency.[17] Owing to the favorable advantages, CILs are widely used in diverse separation processes,[18-20] especially their application in enantioselective extraction became an important issue in research in recent years. A pioneering work to separate phenylalanine racemate through chiral ligand-exchange liquid-liquid extraction using Cu^{2+} modified amino acid ionic liquid (AAIL) done by Tang et al achieved an excellent enantiomeric excess value reaching up to 50.6% in single-stage extraction.[21] In other relevant research, the separation efficiency was further improved by introducing tropine-based cation into the AAIL.[22] Despite these results show that CIL-based extraction is a very promising chiral separation technology, the difficulty in

further recovery of the products from the metal ligand still remains to be a problem.[21] More importantly, metal contamination on products especially pharmaceuticals may become a critical hurdle to limit the industrial application of CILs. An effective way to overcome the defects of chiral ligand-exchange extraction is to exploit the chiral recognition capabilities of CILs directly without the use of coordinated metals,[23] which meanwhile sets higher requirement for the configuration and chemistry of CILs to match specific chiral compound and has rarely been reported. Considering in some discussions earlier, quantum chemistry calculation has been successfully used to investigate the structure-function relationship of CILs and predict their performance in extraction separation of phenolic homologs,[24] we are inspired to expect that this approach may also provide guidance to the selection of CIL for enantioselective extraction. Despite other computational methods such as conductor-like screening model (COSMO) calculation is available to predict behaviors of ionic liquids in complex systems by considering the charge distribution on molecular surfaces,[25, 26] it's not applicable to discriminate optical isomers in this work as the difference in charge distributions between molecules only differing in conformations is usually very slight.[27]

With the aim to create a high-performance and green separation process for amlodipine, we report an experimental research combined with quantum chemistry calculations to develop a CIL-based liquid-liquid extraction system in this work. AAILs derived from natural amino acids were chosen for investigation as they were low-cost and biodegradability.[21, 28] A pre-screening of AAILs was carried out by quantum chemistry calculation, and the predictive capability of the theoretical calculations was further validated by experimental data. The impacts of organic solvent, solution pH, concentration of the

substrates and extraction temperature on the separation efficiency, along with the recycling of AAIL were systematically investigated. It is prospected the approach proposed in the present work may extend the application of CILs in chiral separations.

Methods

Quantum chemistry calculation details

Quantum chemistry calculations in this work were performed with Gaussian 16 software.[29] The hybrid Becke 3-Lee-Yang-Parr (B3LYP) exchange-correlation functional[30] and the density functional theory (DFT)[31] with 6-31+G(d,p) basis set were employed. And dispersion-corrected[32] DFT at B3LYP-D3/6-311+G(d,p) level of theory is also applied to determine the reasonable geometries. No constraint was applied to the geometry optimizations and all optimized geometries were verified as local minimums on the potential energy surface by vibrational frequency calculations. The geometries of amlodipine enantiomers, anions and cations of AAILs were produced by optimization and modification based on the previously published configurations.[33-36] The optimization of ion pairs was done by placing the anions at different positions around the cations to construct different initial conformations and then optimizing them respectively. Conformation with the lowest energy was taken as global minimum for the AAIL. The initial conformations of amlodipine-AAIL complexes were constructed based on the molecular electrostatic potentials of the enantiomers and the ion pairs. Subsequently, the global minimums of all complexes were explored by geometry optimizations on these initial conformations. Interaction energies between amlodipine enantiomers and AAILs were calculated and corrected by basis set

superposition errors (BSSE) obtained by the counterpoise procedure method[37] and zero-point energies (ZPE) obtained within the harmonic approximation. To get further insight into the interactions, atoms in molecules (AIM) analysis was also performed for the optimized amlodipine-AAIL complexes by AIMALL program.[38]

Chemicals and analytical method

Racemic amlodipine was purchased from Dalian Meilun Biotech Co. Ltd (Liaoning, China). 1-butyl-3-methylimidazolium L-glutamate ([Bmim][Glu], 97%), 1-ethyl-3-methylimidazolium L-glutamate ([Emim][Glu], 97%), 1-butyl -3-methylimidazolium L-serinate ([Bmim][Ser], 97%), 1-ethyl-3-methylimidazolium L-serinate ([Emim][Ser], 97%), 1-butyl-3-methylimidazolium L-phenylalanate ([Bmim][Phe], 97%) and 1-ethyl-3-methylimidazolium L-phenylalanate ([Emim][Phe], 97%) were purchased from Chengjie Chemical Co. Ltd (Shanghai, China). n-decanol (98%) and n-hexanol (98%) were purchased from Aladdin Reagent Co. Ltd (Shanghai, China). 1,2-dichloroethane (AR, 99.0%), dichloromethane (AR, 99.5%), n-octanol (AR, 99.0%), sodium acetate (NaAc, AR, 99%) and acetate (HAc, AR, 99.5%) were purchased from Sinopharm Chemical Reagent Co. Ltd (China). NaAc/HAc buffer solutions in different pH ranges were prepared by mixing of sodium acetate and acetate solutions (both 0.3 mol/L) in proper proportions, and the pH measurements were performed with a pHS-3C digital pH-meter (LeiCi, Shanghai, China).

Concentration of amlodipine enantiomers in organic phase was detected by high-performance liquid chromatography (HPLC, Agilent 1260 Infinity LC system). An EnantioPak SCDP column (5 μm, 4.6 × 250 mm^2) was used with the mobile phase made up

of n-hexane (containing 0.1% trifluoroacetic acid) and ethanol (85/15, v/v). The flow rate of the mobile phase was set to be 1 mL/min, and the detection on amlodipine was performed by defined wavelength at 237 nm.

Extraction and backward extraction process

In this work, all AAILs were diluted before use, as the pure AAILs were highly viscous near room temperature. The aqueous phase was prepared by dissolving a known amount of AAIL into NaAc/HAc buffer solution, and the organic phase was prepared by dissolving racemic amlodipine into halohydrocarbon or aliphatic alcohol. The aqueous phase and the organic phase at the same volume were put together into a shake flask, shaken isothermally at 220 rpm for 3 hours when the extraction equilibrium has already been achieved as shown in Supplementary Figure 1 (take n-decanol-buffer/[Bmim][Glu] system for example), and settled for 30 minutes. The organic phase was then taken out of the flask without disturbing the aqueous phase and detected by HPLC to determine the concentration of amlodipine. Due to all organic solvents used in this work were almost immiscible with water, the concentration of amlodipine in the aqueous phase could be determined by mass balance method.[39-41] All experiments were repeated at least three times and the errors in distribution coefficients were less than 5%. The distribution coefficient and enantioselectivity were calculated by the following equations,

$$D_S = \frac{C_{So}}{C_{Sa}} \quad (1)$$

$$D_R = \frac{C_{Ro}}{C_{Ra}} \quad (2)$$

$$\alpha = \frac{D_S}{D_R} \quad (3)$$

where C_{So} and C_{Ro}, C_{Sa} and C_{Ra} refer to the concentration of (*S*)-amlodipine and (*R*)-amlodipine in the organic phase, concentration of (*S*)-amlodipine and (*R*)-amlodipine in the aqueous phase, respectively. D_S and D_R refer to the distribution coefficients of (*S*)-amlodipine and (*R*)-amlodipine, and α refers to the enantioselectivity.

To assess the mutual solubility between AAIL and organic solvent during the extraction process, blank extraction experiments were conducted. All experimental conditions were kept the same as mentioned above, except that amlodipine racemate was not added to exclude the interference for detection. After phase equilibrium had been reached, the content of AAIL in the organic solvent was determined on a 752PC UV–vis spectrophotometer (Shanghai spectrum, China). The results show that AAIL dissolved in the organic solvent is negligible. Take n-decanol-buffer (pH=5.5)/[Bmim][Glu] biphasic system for example, the mole fraction of AAIL in the organic solvent is only nearly 0.01% (Supplementary Figure 2).

After the extraction process, the AAIL containing aqueous phase loaded with amlodipine was separated from the organic phase and used for backward extraction. The aqueous phase was mixed with n-decanol (1:1, v/v) and shaken vigorously under 298.15 K for 2 hours to reach phase equilibrium, then settled for half an hour. The aqueous phase and the organic phase were separated from each other, and the aqueous phase was reused in the extraction process. The schematic representation of the experimental procedure is shown in Figure 2.

Results and Discussion

Hunting AAILs for the separation of amlodipine by quantum chemistry calculations

In this work, the candidate AAILs are generated by combining the imidazolium cations $Emim^+$, $Bmim^+$ with amino-acid derived anions Glu^-, Phe^- and Ser^-. At the beginning, [Bmim][Glu] will be proposed as a representative to illustrate the chiral recognition mechanisms of AAILs. The optimized geometry of the complex formed by [Bmim][Glu] and (*R*)-amlodipine at B3LYP/6-31+G(d,p) level of theory is displayed in Figure 3a. There are three explicit hydrogen bonds represented by dash lines formed between them, and both the cation and the anion of the AAIL are involved in these hydrogen bonding interactions. The oxygen atoms contained in the γ-carboxyl of Glu^- are labeled as O_{66} and O_{67} respectively, and they both act as hydrogen bond acceptors for (*R*)-amlodipine. The corresponding hydrogen donor for O_{66} is the hydrogen atom contained in the amino group of (*R*)-amlodipine, and that for O_{67} is the hydrogen atom contained in the methyl, which is connected to the dihydropyridine ring of (*R*)-amlodipine. Besides, a third hydrogen bond is found between the hydrogen atom on the butyl group of $Bmim^+$ and the carbonyl oxygen atom of (*R*)-amlodipine, which is labeled as O_{31}. According to the results of AIM analysis, the electron densities (ρ_c) on bond critical points (BCPs) of N_{44}-H_{46}…O_{66}, C_{84}-H_{85}…O_{31} and C_{19}-H_{22}…O_{67} are 0.0165, 0.0113 and 0.0058 a.u. respectively, and the corresponding Laplacian values ($\nabla^2\rho_c$) are 0.0653, 0.0423 and 0.0283 a.u.. All these values are within the typical range of hydrogen bond (0.002-0.035 a.u. for ρ_c, and 0.024-0.139 a.u. for $\nabla^2\rho_c$).[42]

In the optimized geometry of (*S*)-amlodipine-[Bmim][Glu] (Figure 3b), interaction between the γ-carboxyl of Glu^- and the amino group of (*S*)-amlodipine, and that between the side chain of $Bmim^+$ and the carbonyl oxygen atom O_{31} of the enantiomer can still be found. Nevertheless, due to the steric effect between the chlorphenyl group of (*S*)-amlodipine and the butyl group of $Bmim^+$, the orientation between the side chains of $Bmim^+$ and O_{31} is different from that in (*R*)-amlodipine-[Bmim][Glu]. As is shown, the hydrogen atom to interact with O_{31} is located in the methyl rather than the butyl of $Bmim^+$. Moreover, there's no hydrogen bond between the γ-carboxyl of Glu^- and the hydrogen atoms in the methyl of (*S*)-amlodipine as in (*R*)-amlodipine-[Bmim][Glu], because they move further from each other also by influence of the steric effect. The length of C_{80}-H_{82}…O_{31} in (*S*)-amlodipine-[Bmim][Glu] is 2.43 Å, and it is relatively longer than C_{84}-H_{85}…O_{31} in (*R*)-amlodipine-[Bmim][Glu] by 0.12 Å, indicating the hydrogen bonding interaction between the side chain of $Bmim^+$ and the carbonyl oxygen atom O_{31} in (*R*)-amlodipine-[Bmim][Glu] should be stronger than in (*S*)-amlodipine-[Bmim][Glu], since a shorter length is usually more favorable to forming a more stable hydrogen bond. The inference is further confirmed by the results of AIM analysis, because the values of ρ_c and $\nabla^2\rho_c$ for C_{80}-H_{82}…O_{31} are 0.0092 and 0.0357 a.u. respectively, and both of them are smaller than those of C_{84}-H_{85}…O_{31}. The length of N_{44}-H_{46}…O_{67} in (*S*)-amlodipine-[Bmim][Glu] is also longer than N_{44}-H_{46}…O_{66} in (*R*)-amlodipine-[Bmim][Glu], and further analysis of AIM reveals N_{44}-H_{46}…O_{66} possesses higher stability as well, with slightly larger ρ_c and $\nabla^2\rho_c$ than N_{44}-H_{46}…O_{67} (0.0162 a.u. for ρ_c and 0.0635 a.u. for $\nabla^2\rho_c$). By this way, it can be concluded that the hydrogen bonding network between [Bmim][Glu] and (*R*)-amlodipine is stronger

than that between [Bmim][Glu] and (*S*)-amlodipine. The result implies the AAIL is likely to recognize (*R*)-amlodipine preferentially. Furthermore, the interaction energies for [Bmim][Glu] to interact with (*R*)-amlodipine and (*S*)-amlodipine are -50.64 and -42.64 kJ/mol, respectively. Considering a more negative energy corresponds to stronger interactions, the same result can be attained that [Bmim][Glu] interacts more strongly with (*R*)-amlodipine, herein its potential recognition effect for (*R*)-amlodipine is more evident. The above analyses approve that hydrogen bonding interactions are crucial in determining the enantioselective recognition capability of AAIL. Similarly, in some discussions earlier, the essential role of hydrogen bonds to recognize structurally similar bioactive compounds in ionic liquid-mediated extraction has also been confirmed.[24, 43, 44]

Optimized geometries of complexes formed by amlodipine enantiomers and other five AAILs at B3LYP/6-31+G(d,p) level are summarized in Supplementary Figure 3-7. By comparing these conformations, it can be found that the active sites for amlodipine to interact with different AAILs are uniform, as has been revealed in the above discussion about [Bmim][Glu]. It represents that amlodipine has analogous interaction mechanism with these AAILs. Moreover, the cations interact with the enantiomers mainly through the side carbon chains, which are also responsible for steric effects. However, the active sites for different amino-acid derived anions to interact with amlodipine are somewhat different from each other, due to the subtle change in their compositions and structures.

Interaction energies between different AAILs and amlodipine enantiomers at B3LYP/6-31+G(d,p) level are listed in Table 1, where ΔE_R and ΔE_S refer to energies for AAILs to interact with (*R*)-amlodipine and (*S*)-amlodipine respectively, and the quantity ΔE

calculated by subtracting ΔE_R from ΔE_S represents the energy difference between ΔE_R and ΔE_S. As is shown, ΔE_R and ΔE_S for different AAILs are all negative, and vary from -42.35 to -63.23 kJ/mol. Except for [Bmim][Glu], the values of ΔE_R for other three AAILs including [Bmim][Ser], [Emim][Ser] and [Bmim][Phe] are also more negative than the corresponding ΔE_S. The result indicates that these AAILs all interact more strongly with (*R*)-amlodipine than with (*S*)-amlodipine, so it is theoretically possible that they all exhibit preferable recognition effect towards (*R*)-amlodipine. Unlike the above four AAILs, [Emim][Glu] and [Emim][Phe] are expected to recognize (*S*)-amlodipine preferably, because the values of ΔE_R for these two AAILs are less negative than ΔE_S, meaning stronger interactions with (*S*)-amlodipine. By further comparing ΔE for all the AAILs, it can be seen this value for [Bmim][Glu] is very remarkable. It accounts for nearly 20% of the total energy for this AAIL to interact with (*S*)-amlodipine, and its absolute value is at least two times that of [Bmim][Ser], [Emim][Ser], [Bmim][Phe] and [Emim][Phe]. It implies the recognition capability of [Bmim][Glu] should be much stronger than the other AAILs, because a larger energy difference between ΔE_R and ΔE_S represents a more significant discrepancy between the stabilities of (*S*)-amlodipine-AAIL and (*R*)-amlodipine-AAIL complexes, which is more beneficial to the separation.

We also calculated the interaction energies based on amlodipine-AAIL complexes (Supplementary Figure 8-13) optimized at B3LYP-D3/6-311+G(d,p) level, and the results are summarized in Table 1. As is shown, the values of ΔE_R and ΔE_S on this level are significantly lower than those on B3LYP/6-31+G(d,p) level by 63.87-99.08 and 64.51-96.99 kJ/mol, respectively, representing that the incorporation of Grimme's dispersion correction (D3) in

the DFT based exchange-correlation functions can fairly well consider the dispersion effects.[45, 46] The values of ΔE for [Bmim][Glu], [Bmim][Ser] and [Emim][Ser] are positive, and that for [Emim][Glu] stay negative, just the same as that observed on B3LYP/6-31+G(d,p) level, again suggesting their preferable recognition effect for (*R*)-amlodipine and (*S*)-amlodipine, respectively. Most importantly, the absolute value of ΔE for [Bmim][Glu] nearly doubled compared to that calculated on B3LYP/6-31+G(d,p) level, and is more significantly higher than for other AAILs, highlighting its potential superior enantioselective recognition capability for amlodipine racemate.

Table 1. BSSE and ZPE corrected interaction energies calculated on B3LYP/6-31+G(d,p) and B3LYP-D3/6-311+G(d,p) levels of theory (unit: kJ/mol)

Validation of quantum chemistry calculations

As is mentioned earlier, quantum chemistry calculation has been successfully used to predict the phase behavior of phenolic homologs in CIL-based extraction systems.[24] However, as far as we know, there is still no report about the predictive capability of quantum chemistry calculations on the separation of chiral compounds using CILs. Therefore, it is necessary to validate whether the computational approach would be fit for the enantioselective systems with experimental data.

On this account, a series of biphasic systems comprising different AAILs were constructed to experimentally test the chiral recognition capabilities of these chiral extractants. The resulting distribution coefficients and corresponding enantioselectivities are displayed in Figure 4a. It can be seen, when [Bmim][Glu], [Bmim][Ser] and [Emim][Ser] are

used as chiral extractants, the distribution coefficients of (*S*)-amlodipine are visibly larger than (*R*)-amlodipine, and the enantioselectivities are measured as 1.35, 1.11, and 1.05, respectively. This phenomenon confirms that the three AAILs all interact more strongly with (*R*)-amlodipine than with (*S*)-amlodipine, herein their preferential recognition effects towards (*R*)-amlodipine predicted by quantum chemistry calculation are identified. When [Emim][Glu] is employed, the distribution coefficient of (*R*)-amlodipine turns out to be higher than that of (*S*)-amlodipine, and enantioselectivity below 1 is observed, because of its unique preferable recognition effect for (*S*)-amlodipine. The phenomenon that [Emim][Glu] and [Bmim][Glu] exhibit opposite recognition effect to each other is mainly attributed to the difference in their lengths of carbon chains in the cations, which greatly influences the steric effect between the ion pairs and the enantiomers, thus leading to distinct amlodipine-AAIL complex conformations (Figure 1, Supplementary Figure 3). In the other two Phe^--based AAILs containing systems, the distribution coefficients of (*R*)-amlodipine are very close to those of (*S*)-amlodipine, revealing these AAILs exhibit very poor chiral recognition abilities for amlodipine. The reason is that both [Bmim][Phe] and [Emim][Phe] have quite close binding capabilities for different amlodipine enantiomers, with absolute value of ΔE being only 1.75 and 2.02 kJ/mol on B3LYP/6-31+G(d,p), 1.39 and 1.08 kJ/mol on B3LYP-D3/6-311+G(d,p), as shown in Table 1. Despite there is no meaning in determining the recognition tendency of [Bmim][Phe] and [Emim][Phe], the result still approves that a larger interaction energy difference is more favorable for the separation process.

In summary, enantioselectivities of these AAILs investigated in this work are in the order that [Bmim][Glu] > [Bmim][Ser] > [Emim][Ser] > [Bmim][Phe] ≥ [Emim][Phe] >

[Emim][Glu]. It is noteworthy that when the enantioselectivity is plotted versus ΔE (Figure 4b), an approximate linear relationship is shown between the two quantities, both on B3LYP/6-31+G(d,p) and B3LYP-D3/6-311+G(d,p) levels of theory. The result proves that the pre-screening of AAILs by quantum chemistry calculations based on interaction energies is applicable to the present work.

Extraction of amlodipine with and without [Bmim][Glu] as chiral extractant

From the above theoretical calculation and experimental results, it has been verified that [Bmim][Glu] is a promising chiral extractant for amlodipine. In the subsequent studies efforts would be focused on developing an efficient enantioselective system using [Bmim][Glu] as the chiral extractant. For this purpose, a collection of organic solvents were combined with the [Bmim][Glu]-buffer solution to construct different biphasic systems, and phase behaviors of amlodipine enantiomers in these systems were investigated.

Table 2. Distribution coefficient and enantioselectivity for different biphasic systems[a]

From the results summarized in Table 2, it can be seen the distribution coefficients of amlodipine enantiomers in halohydrocarbon (1,2-dichloroethane/dichloromethane) containing systems are relatively smaller than in other systems, with or without the addition of [Bmim][Glu], indicating the affinities of 1,2-dichloroethane and dichloromethane for amlodipine are somewhat weaker than aliphatic alcohols. In aliphatic alcohols containing systems, the distribution coefficients of amlodipine enantiomers are in the order that n-hexanol > n-octanol > n-decanol, which is consistent with the polarities of these aliphatic

alcohols. When [Bmim][Glu] is absent, the distribution coefficients of (*R*)-amlodipine and (*S*)-amlodipine in n-hexanol-buffer reach up to 75.82 and 79.61. While in n-octanol-buffer, the distribution coefficients for (*R*)-amlodipine and (*S*)-amlodipine decrease dramatically to 36.33 and 37.91 respectively, and those in n-decanol-buffer are even lower. When [Bmim][Glu] is added, the trend still holds as shown in Table 2. These results reveal that the property of organic solvent has a great effect on the phase behavior of amlodipine, and aliphatic alcohols of higher polarities would have stronger affinities for amlodipine enantiomers. More importantly, it can also be seen that the addition of [Bmim][Glu] lowers the distribution coefficients no matter in aliphatic alcohol or in halohydrocarbon containing systems, implying there are strong intermolecular interactions between [Bmim][Glu] and amlodipine enantiomers, which drive the enantiomers into the aqueous phase.

In n-decanol and n-octanol containing systems, the addition of [Bmim][Glu] is observed to promote the enantioselectivities to different degrees. When [Bmim][Glu] is absent, the enantioselectivities in n-decanol-buffer and n-octanol-buffer are only 0.97 and 1.04. While after the addition of [Bmim][Glu], they increase to 1.35 and 1.21 respectively, indicating [Bmim][Glu] dose have a prominent chiral recognition effect for (*R*)-amlodipine as has been predicted by quantum chemistry calculations. By contrast, in other organic solvents containing systems, the addition of [Bmim][Glu] does not make very distinct difference in enantioselectivity. The reason might be that the affinities of halohydrocarbons and n-hexanol towards amlodipine enantiomers are either too small or too large to achieve a moderate distribution of the enantiomers between the aqueous phase and the organic phase. In halohydrocarbons containing systems, the smaller distribution coefficients mean the

concentration of amlodipine in the aqueous phase was higher than in other systems, so the probability that [Bmim][Glu] was occupied by competing (*S*)-amlodipine increased. As for in n-hexanol containing system, the relatively larger distribution coefficients declare the concentration of amlodipine in the aqueous phase was lower than other two aliphatic alcohol containing systems, herein the sufficient interaction between (*R*)-amlodipine and [Bmim][Glu] was blocked. The results stress the importance of choosing the modest organic solvent for extraction separation process.

Influence of solution pH on the enantioselective extraction of amlodipine

For this part, n-decanol-buffer/[Bmim][Glu] system in which the aqueous solutions were weakly acid with pH values ranging from 3.5 to 6.0 was used to investigate the effect of solution pH on the enantioselective extraction process. The distribution coefficient and enantioselectivity were plotted versus the pH of the aqueous solution in Figure 5. Apparently, the distribution coefficient shows a strong dependence on acidity. The increase in solution pH results in a continuous growth in distribution coefficients for both enantiomers. Amlodipine is known as a weak alkaline compound and its pKa is equal to 8.6.[47] In aqueous solution, it could exist in either a molecular form or a cationic form depending on the deprotonation and protonation behavior of the primary amino group. According to the following Henderson-Hassaelbach equation,[48]

$$pH = pKa + \log\left(Base[B]/Acid[BH^+]\right) \qquad (4)$$

when the pH value is improved, the percentage of monomers in molecular form increases gradually, implying more amlodipine monomers are ready to dissolve in the organic phase. For this reason, the variation in distribution coefficients of amlodipine is estimated to be

reasonable.

The buffer solution pH also greatly affects the enantioselectivity. When the solution pH is in the range of 3.5 to 5.5, the enantioselectivity grows continuously and reaches its maximum at pH=5.5. However, further increase in solution pH brings about a severe decrease in enantioselectivity, and it drops to only 1.06 when the pH is 6.0. Actually, along with the rapid increase in distribution coefficient, the amount of amlodipine in the aqueous phase declines very quickly, and the concentration of amlodipine at pH=6.0 equals only nearly half of that at pH=5.5. The extra low concentration of amlodipine under increased pH would impair the interactions between the enantiomers and AAIL so that the dramatic decrease in enantioselectivity is observed. From above, it can be concluded that the solution pH has a great effect on the extraction process by influencing the existence form of amlodipine monomers, and pH=5.5 would be appropriate for the separation process.

Influence of the concentration of AAIL on the enantioselective extraction of amlodipine

To investigate the influence of the concentration of AAIL on the extraction efficiency, aqueous solutions containing [Bmim][Glu] with different AAIL concentrations varying from 0.01 to 0.20 mol/L were prepared and applied to the extraction process, and the results are summarized in Figure 6. Along with the increase in the concentration of [Bmim][Glu], the distribution coefficients for both enantiomers decrease because a higher concentration of [Bmim][Glu] leads to stronger interactions with amlodipine, and consequently higher concentration of amlodipine enantiomers in the aqueous phase. It is also found the enantioselectivity increases under low [Bmim][Glu] concentration and reaches the peak at

c_{AAIL}=0.025 mol/L. However, further increase in the concentration of [Bmim][Glu] would reduce the enantioselectivity, because non-preferential recognition for (*S*)-amlodipine is included.

Influence of initial concentration of racemic amlodipine on the enantioselective extraction of amlodipine

The effect of initial concentration of racemic amlodipine on the extraction process is shown in Figure 7, where the initial concentration was in the range of 0.5 to 3.0 g/L. It can be observed, both the distribution coefficient and the enantioselectivity rise firstly and then decline with the increase in the initial concentration of amlodipine. The distribution coefficients come to the maximum values when $c_{amlodipine}$=2.25 g/L, while the enantioselectivity comes to its maximum at $c_{amlodipine}$=2.0 g/L. The result verifies that the initial concentration of amlodipine has an important effect on the phase behavior, and 2.0 g/L would be a suitable initial concentration for amlodipine.

Influence of temperature on the enantioselective extraction of amlodipine

In general, temperature is an important factor influencing the separation efficiency of chiral extraction process. Lower temperature is usually more beneficial to improve the enantioselectivity because interactions between chiral extractants and target molecules usually get weakened under higher temperature, and the chiral recognition effect will be impaired as a result.[40, 49] For this reason, the previously proposed methods for the extraction of amlodipine using conventional extractants such as cyclodextrin and tartaric acid

derivatives all require to be handled at frigid temperature,[10, 11] which brings about intensive energy consumption. As far as we know, enantioselectivities of those methods near room temperature (298.15 K) would not be higher than 1.14.

In this work, the effect of extraction temperature on the phase behavior of amlodipine enantiomers in n-decanol-buffer/[Bmim][Glu] was studied with the window opened from 288.15 to 318.15 K. According to the results listed in Figure 8, enantioselectivity reaching up to 1.38 can be achieved at 288.15 K, whereas it drops only slightly under room temperature and maintains at 1.35 although higher temperature is unfavorable for separation, owing to the superior chiral recognition capability of [Bmim][Glu]. By contrast to other extraction systems comprising conventional chiral extractants, the performance has been significantly improved by the use of AAIL. More importantly, the desirable separation efficiency under room temperature proves the present system is conducive to energy saving and consumption reducing.

Recycling of [Bmim][Glu]

The recycling of ionic liquids is important for developing an economic and environmentally benign separation process. In this work, the recycling of [Bmim][Glu] was achieved by regenerating the aqueous phase through backward extraction, with no need to further purify the AAIL. Note that n-decanol was employed as the organic solvent in backward extraction process mainly for two reasons. Firstly, n-decanol itself is an adequate organic solvent for the enantioselective extraction of amlodipine racemate. To keep the organic solvent consistent in both extraction and backward extraction process is beneficial to establish easy-handling and continuous operations. Secondly, the backward extraction

efficiency is very desirable. The result of HPLC analysis shows that after the backward extraction, the concentration of amlodipine in the aqueous phase is below 0.01 g/L, which is negligible to the initial concentration of amlodipine at 2.0 g/L.

The performance of the reused [Bmim][Glu] containing aqueous phase within 5 cycles is shown in Figure 9. Compared to extraction process using fresh aqueous phase, the enantioselectivity obtained with the regenerated aqueous phase declined a little bit. A reasonable explanation to the phenomenon is that the regenerated aqueous phase is saturated with n-decanol, which may subtly influence the phase equilibrium. It was also confirmed by an additional controlled extraction experiment in which a n-decanol pre-saturated [Bmim][Glu] containing aqueous solution was used. The results indicate that enantioselectivity of amlodipine also descends to about 1.24, just similar to that in regenerated CIL-based system. Nevertheless, considering enantioselectivity in the regenerated system still stays above 1.20 within 5 cycles, and the distribution coefficients in different cycles only change very slightly, it can be deduced that the reused [Bmim][Glu] still remains good separation efficiency for amlodipine.

Conclusions

In this work, a novel enantioselective liquid-liquid extraction system comprised of n-decanol, NaAc/HAc buffer solution and AAIL was proposed for the separation of amlodipine. Quantum chemistry calculations were carried out to give a pre-screening to the candidate AAILs, and revealed that [Bmim][Glu] was supposed to exhibit more preferable chiral recognition effect for amlodipine enantiomers than other studied AAILs. The

theoretical calculations also provide comprehensive insights into the chiral recognition mechanisms of AAILs, and show that hydrogen bonding interactions are essential to the recognition capabilities of AAILs. To validate the theoretical calculations, phase behaviors of amlodipine enantiomers in diverse biphasic systems containing different AAILs were investigated, and we found that the enantioselectivity showed a strong dependence on ΔE. It demonstrates the quantum chemistry calculations are capable to provide reasonable guidance to the screening and design of CILs. Subsequently, the impacts of several important factors on the separation efficiency of amlodipine in the present system were investigated. The results show that under optimal conditions when the initial concentration of [Bmim][Glu] and racemic amlodipine are 0.025 mol/L and 2.0 g/L respectively, the solution pH is 5.5 and the extraction temperature is 288.15 K, enantioselectivity reaching up to 1.38 can be achieved. When operated at 298.15 K, only a small drop in separation efficiency was observed, revealing the present system made less strict demand on temperature than conventional extraction systems containing organic chiral extractants, herein the method was proved to be more energy-efficient. Lastly, the recycling of [Bmim][Glu] by regenerating the AAIL containing aqueous phase through backward extraction was studied, and the experimental data showed that the reused [Bmim][Glu] still remained good separation efficiency. Thus, we have successfully developed a new potential chiral separation process for amlodipine.

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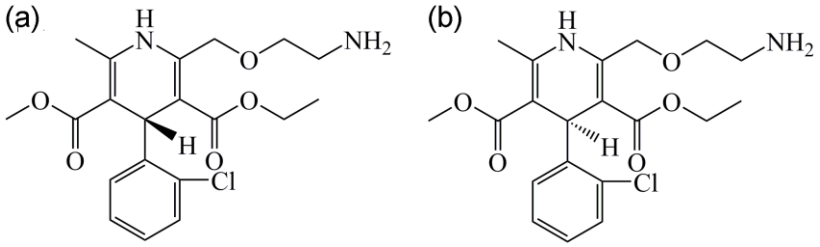

Figure 1. The structures of (a) (*R*)-amlodipine and (b) (*S*)-amlodipine

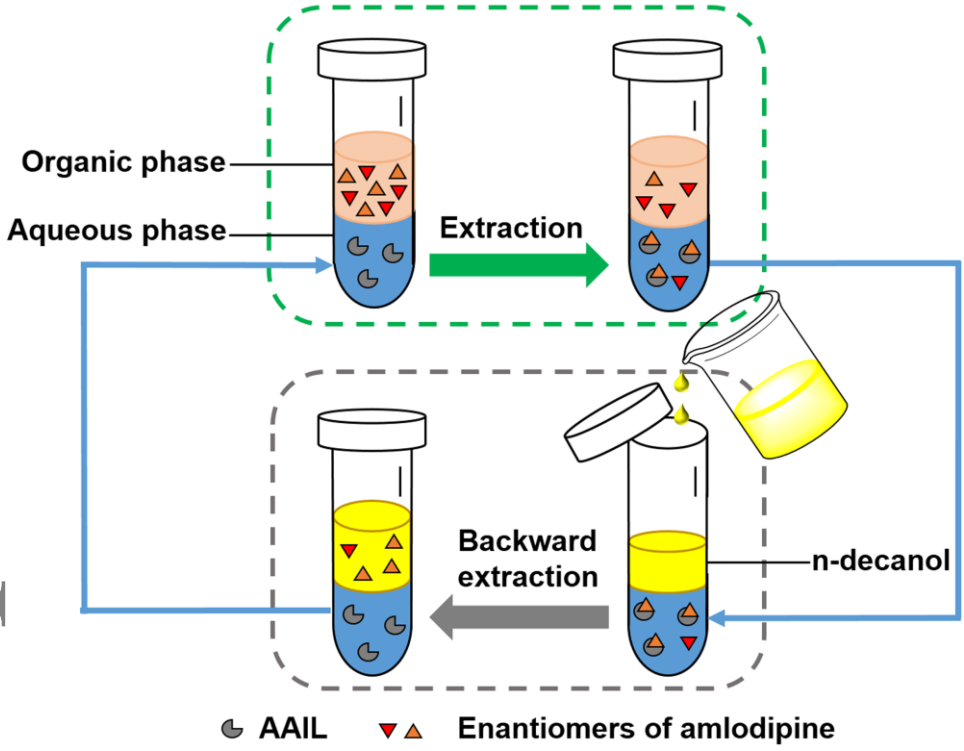

Figure 2. Schematic representation of the experimental procedure

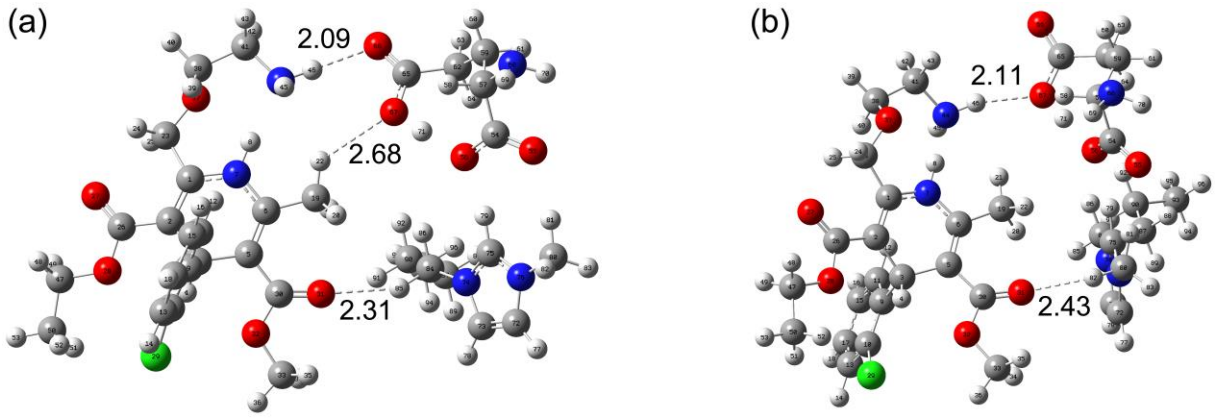

Figure 3. Optimized structures of (a) (*R*)-amlodipine-[Bmim][Glu] and (b) (*S*)-amlodipine-[Bmim][Glu] at B3LYP/6-31+G(d,p) level. All interatomic distances represented by dash lines are in angstroms.

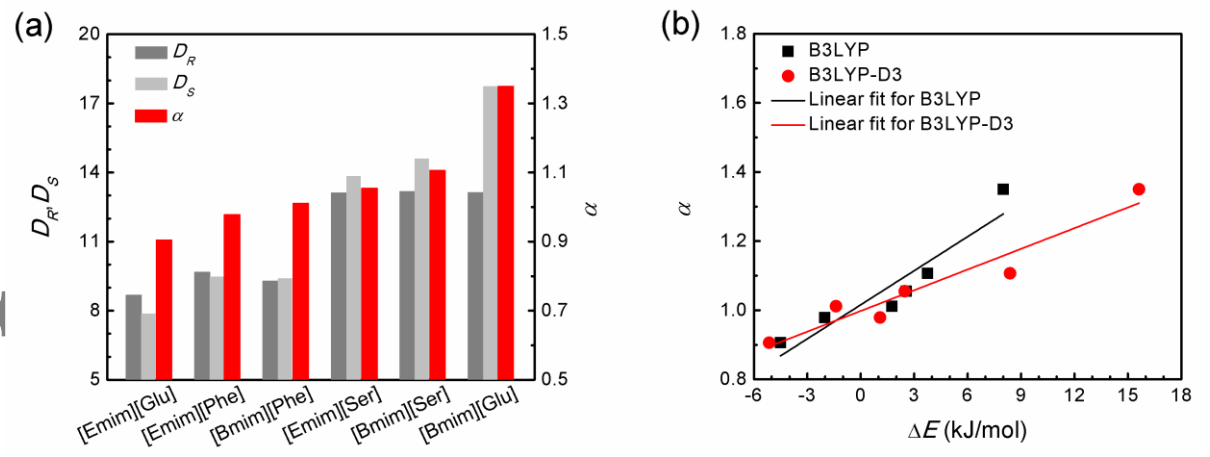

Figure 4. (a) Distribution coefficient and enantioselectivity of amlodipine enantiomers in different n-decanol-buffer/AAIL systems and (b) enantioselectivity plotted versus ΔE calculated on B3LYP/6-31+G(d,p) and B3LYP-D3/6-311+G(d,p) levels of theory. (The initial concentration of racemic amlodipine and AAIL were 2.0 g/L and 0.025 mol/L, respectively. The buffer pH was 5.5. Extraction temperature was 298.15 K. R^2 for linear fit of B3LYP and B3LYP-D3 in (b) are 0.85 and 0.91, respectively.)

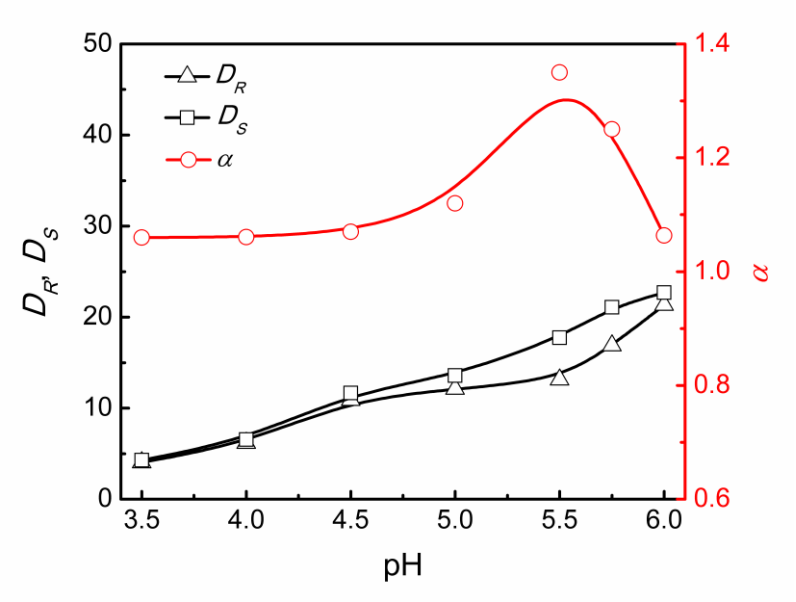

Figure 5. Influence of solution pH on distribution coefficient and enantioselectivity. (The initial concentration of amlodipine and [Bmim][Glu] were 2.0 g/L and 0.025 mol/L, respectively. The temperature was 298.15 K.)

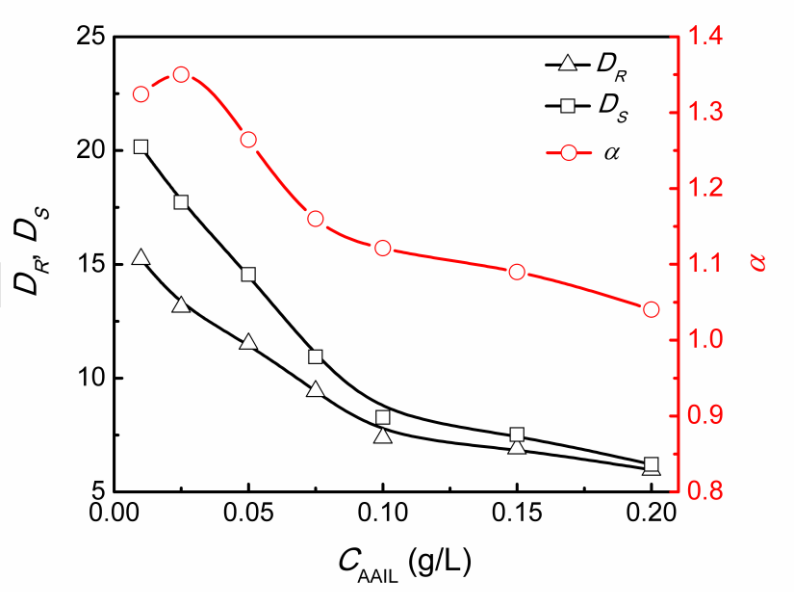

Figure 6. Influence of concentration of AAIL on distribution coefficient and enantioselectivity. (The initial concentration of amlodipine was 2.0 g/L. The solution pH was 5.5. The temperature was 298.15 K.)

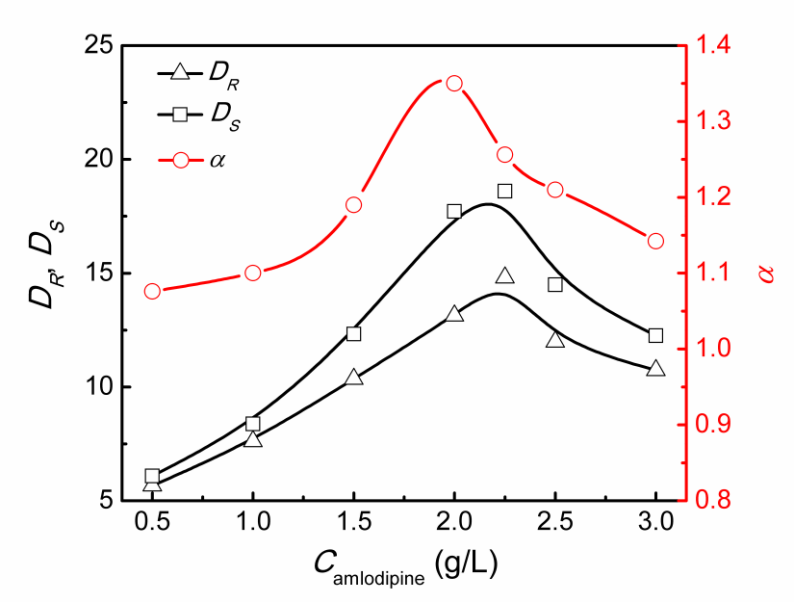

Figure 7. Influence of initial concentration of amlodipine on distribution coefficient and enantioselectivity. (The concentration of [Bmim][Glu] was 0.025 mol/L. The solution pH was 5.5. The temperature was 298.15 K.)

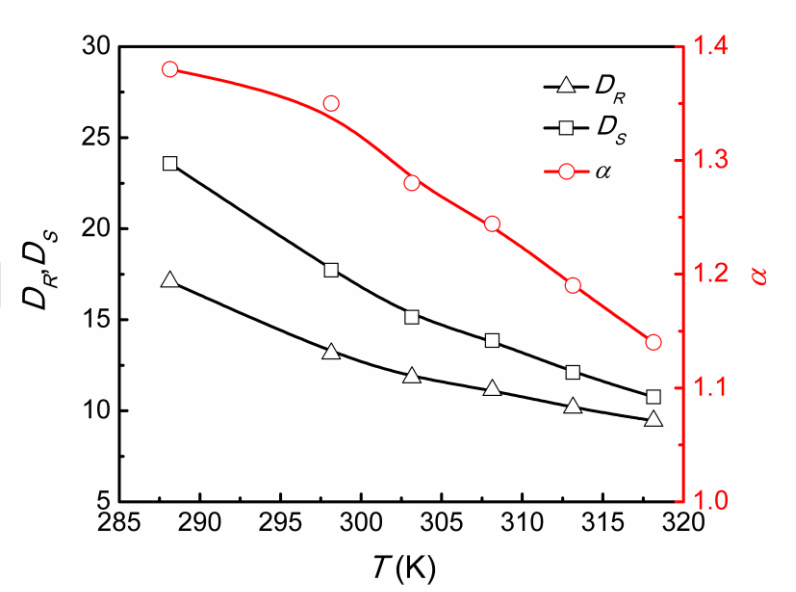

Figure 8. Influence of extraction temperature on the distribution coefficient and enantioselectivity. (The initial concentration of racemic amlodipine and [Bmim][Glu] were 2.0 g/L and 0.025 mol/L, respectively. The buffer pH was 5.5.)

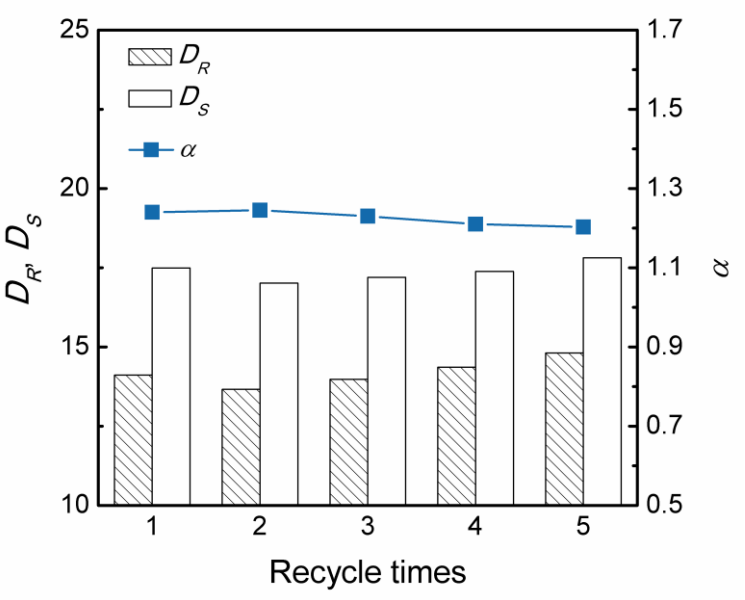

Figure 9. Distribution coefficient and enantioselectivity of amlodipine in different recycle times. (The initial concentration of racemic amlodipine and [Bmim][Glu] were 2.0 g/L and 0.025 mol/L, respectively. The buffer pH was 5.5. The temperature was 298.15 K.)

Table 1. BSSE and ZPE Corrected Interaction Energies Calculated on B3LYP/6-31+G(d,p) and B3LYP-D3/6-311+G(d,p) Levels of Theory (unit: kJ/mol)

AAILs	**B3LYP/6-31+G(d,p)**			**B3LYP-D3/6-311+G(d,p)**		
	ΔE_R	ΔE_S	ΔE	ΔE_R	ΔE_S	ΔE
[Bmim][Glu]	-50.64	-42.64	8.00	-124.20	-108.57	15.63
[Bmim][Ser]	-45.99	-42.25	3.74	-123.62	-115.24	8.38
[Emim][Ser]	-46.57	-44.02	2.55	-131.94	-129.47	2.47
[Bmim][Phe]	-50.30	-48.55	1.75	-144.15	-145.54	-1.39
[Emim][Phe]	-42.35	-44.37	-2.02	-141.43	-140.35	1.08
[Emim][Glu]	-58.73	-63.23	-4.50	-122.60	-127.74	-5.14

Table 2. Distribution Coefficient and Enantioselectivity for different Biphasic Systems[a]

Biphasic systems	D_R	D_S	α
1,2-dichloroethane-buffer/[Bmim][Glu]	2.90	2.91	1.00
1,2-dichloroethane-buffer	5.33	5.33	1.00
dichloromethane-buffer/[Bmim][Glu]	4.19	4.21	1.00
dichloromethane-buffer	8.01	8.08	1.01
n-decanol-buffer/[Bmim][Glu]	13.13	17.73	1.35
n-decanol-buffer	23.15	22.46	0.97
n-octanol-buffer/[Bmim][Glu]	19.97	24.18	1.21
n-octanol-buffer	36.33	37.91	1.04
n-hexanol-buffer/[Bmim][Glu]	55.43	54.91	0.99
n-hexanol-buffer	75.82	79.61	1.05

[a] The initial concentration of racemic amlodipine and chiral extractant were 2.0 g/L and 0.025 mol/L, respectively. The buffer pH was 5.5. The temperature was 298.15 K.