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Feasibility of Ionic Liquids as Extractants for Selective Separation of Vitamin D_3 and Tachysterol$_3$ by Solvent Extraction

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ABSTRACT: A selective separation of vitamin D_3 and tachysterol$_3$ by solvent extraction with 7 organic solvents and 11 ionic liquids (ILs) has been reported. Among organic solvents sulfolane showed optimal extraction performance, giving only a selectivity of 1.44 for tachysterol$_3$ over vitamin D_3. ILs with unsaturated bonds demonstrated high selectivity probably due to their different $\pi-\pi$ interactions with the two compounds. A pyrrolidinium-based ionic liquid, for example, [BMPr][NTf$_2$], provided the highest selectivity up to 1.77. Acceptable selectivity and distribution coefficients were observed by a combination of organic solvents and ILs as extracting agents. In this work, the effects of concentrations, anions, cations, and substituent of ILs were investigated, which may provide a rational strategy for the design of novel ILs for extractive separation of structural analogues. The purification and recovery of vitamin D_3 via continuous multistage extractions were simulated, indicating that IL-based liquid−liquid extraction might be superior to traditional organic solvents in practical production.

KEYWORDS: *vitamin D_3, tachysterol$_3$, liquid−liquid extraction, organic solvents, ionic liquids, continuous multistage extraction*

INTRODUCTION

Natural bioactive products from biomass have received increasing attention for many years due to their health-promoting benefits and their promising application in drugs and food additives.[1] However, structure-similar homologues existing together with the target compounds usually possess opposite physiological activities. As a result, the separation process is indispensable in obtaining high-purity products and is most challenging in that these compounds are usually similar in structure and thermodynamic properties.

Vitamin D_3 (Figure 1a), also known as cholecalciferol, is a kind of fat-soluble secosteroid that is vital in sustaining the health of animals and humans[2−4] and is widely considered as a food additive and health care product. After metabolization in the liver and kidney sequentially, vitamin D_3 transforms into activated vitamin D_3 (1α,25-(OH)$_2$-vitamin D_3), which is of great significance in biological activities such as the regulation of calcium metabolism and immune function.[5,6] With favorable therapeutic indices such as high efficacy and low toxicity, activated vitamin D_3 and its analogues are used as drugs for various human diseases including secondary hyperparathyroidism, osteoporosis, and psoriasis.[7] In industry, vitamin D_3 is generally prepared through a phototransformation process,[8] which, unfortunately, simultaneously produces undesired structure-similar byproducts including tachysterol$_3$ and lumisterol$_3$. The only difference of vitamin D_3 and tachysterol$_3$ in their chemical structures lies in the position of double bonds, as shown in Figure 1. As a result, their separation is not easy to realize. Currently, few methods have been reported for removal of tachysterol$_3$ from vitamin D_3 except column chromatography,[9] crystallization,[10] molecular distillation,[11] and supercritical fluid chromatography.[12] Column chromatography is no doubt applicable but has several drawbacks such as low loading capacity, large solvent consumption, and high energy consumption for solute recovery. Crystallization is manipulated by a tedious procedure and is also not cost-efficient due to the compounds' slight difference in solubility, unsatisfactory recovery, and purity. Either molecular distillation or supercritical fluid chromatography requires huge investment in equipment and their productivity and capacity are limited. As a consequence, it is meaningful and desirable to develop an efficient separation methodology.

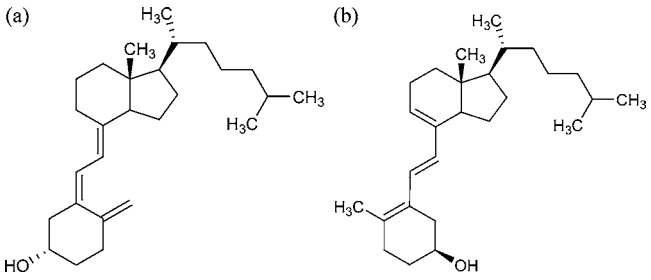

Figure 1. Structures of vitamin D_3 (a) and tachysterol$_3$ (b).

Ionic liquids (ILs) have received explosive interest as alternative organic solvents for their unique physical and chemical properties, for example, negligible vapor pressure, high thermal and chemical stabilities, nonflammability, and functional tunability.[13−16] ILs are also devisable solvents, and their physicochemical properties are tunable by molecular structure optimizations.[17,18] Their polarity and hydrophobicity, as well as hydrogen bond acidity and basicity, can be finely tailored to meet specific applications. Apart from the usage in various chemical reactions,[19] ILs have also been used for the

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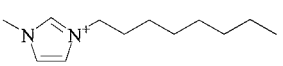
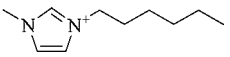
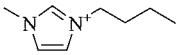
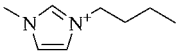
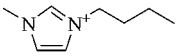
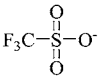
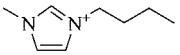
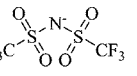
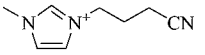
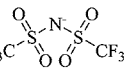
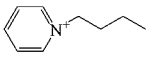
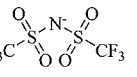
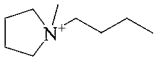
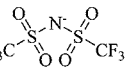
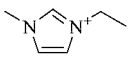
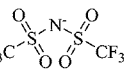
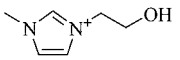
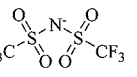
Table 1. Chemical Structures of ILs in This Study and Their Abbreviated Names

Abbreviation	Name	Cation	Anion
[OMIm][BF_4]	1-octyl-3-methylimidazolium tetrafluoroborate		
[HMIm][BF_4]	1-hexyl-3-methylimidazolium tetrafluoroborate		
[BMIm][BF_4]	1-butyl-3-methylimidazolium tetrafluoroborate		
[BMIm][PF_6]	1-butyl-3-methylimidazolium hexafluorophosphate		
[BMIm][TfO]	1-butyl-3-methylimidazolium trifluoromethanesulfonate		
[BMIm][NTf_2]	1-butyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide		
[CPMIm][NTf_2]	1-butyronitrile-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide		
[BPy][NTf_2]	1-butylpridinium bis((trifluoromethyl)sulfonyl)imide		
[BMPy][NTf_2]	1-butyl-1-methylpyrrolidinium bis((trifluoromethyl)sulfonyl)imide		
[EMIm][NTf_2]	1-ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide		
[HOEtmim][NTf_2]	1-(2'-hydroxylethyl)-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide		

extraction of metal ions,[20,21] aromatic compounds,[22,23] phenolic compounds,[24,25] organic acids,[26] amino acids,[27] and the removal of sulfur species from diesel,[28] etc.

In recent years, ILs have been proven effective extractants in the separation of paraffins and aromatics by liquid−liquid extraction when compared with conventional organic solvents. [mebupy][BF_4] and [mebupy][CH_3SO_4] have been tested to be more suitable for extraction of toluene from toluene/heptane mixtures. Both equilibrium distribution coefficients and toluene/heptane selectivities with ILs were even 1.5−2.5 times higher than those with the most industrially used sulfolane.[29] In our previous work, selective separation of phenolic bioactive homologues using IL-based liquid−liquid extraction demonstrated an unprecedented selectivity of 21.3, and hydrogen bond interaction of the ILs was employed as a selection guide to preferentially separate one of the homologues.[30,31] Besides, a high-performance extractive separation of aqua-/lipo-soluble bioactive compounds such as ginkgolide homologues and isoflavone homologues with IL-based biphasic systems was reported.[32,33]

In the present study, we report the feasibility of selective extraction of vitamin D_3 and tachysterol$_3$ by using IL-based extractant, and the effects of concentrations, anions, cations, and substituent of ILs on the extractive performance were investigated. The extraction behavior in the IL systems was compared to that obtained in organic solvents, and the theoretical purity and recovery of vitamin D_3 by continuous multistage extractions were also simulated to demonstrate the superiority of using ILs as extractants for selective separation of vitamin D_3 and tachysterol$_3$. The separation of homologues that differ in the position of double bonds is quite common in chemical engineering. The mechanism of selective extraction studied in this work would provide guidelines that contribute to the selection and design of required extracting solvents.

MATERIALS AND METHODS

Materials. With chemical names listed in Table 1, ionic liquids [OMIm][BF_4] (≥99%), [HMIm][BF_4] (≥99%), [BMIm][BF_4] (≥99%), [BMIm][PF_6] (≥99%), [BMIm][TfO] (≥98.5%), [BMIm]-[NTf_2] (≥99%), [CPMIm][NTf_2] (≥99%), [BPy][NTf_2] (≥99%), [BMPr][NTf_2] (≥99%), [EMIm][NTf_2] (≥99%), and [HOEtMim]-[NTf_2] (≥99%) were obtained from the Center for Green Chemistry and Catalysis, LICP, CAS (China). The water content in ILs was determined by Karl Fischer titration and was examined around 0.8% for ILs with $[BF_4]^-$ anions and no more than 0.3% for the others. Crude vitamin D_3 was kindly supplied by Zhejiang Garden Biochemical High-tech Co., Ltd., China, and the overall purity of vitamin D_3 and tachysterol$_3$ determined by HPLC was >65%. Acetonitrile was of chromatographic grade and purchased from

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Tianjin Institute of Chemical Reagents. The other organic solvents used in this work, with purity >99.5%, were of analytical grade and obtained from Sinopharm Chemical Reagent Co., Ltd. All reagents were used as received, without further purification.

Extraction Equilibrium Experiments. The distribution coefficients of vitamin D_3 and tachysterol$_3$ in liquid−liquid biphasic system were determined as follows: a known amount of prepared mixture was dissolved in hexane to form the homogeneous feedstock. The hexane solution and an equal volume of organic solvents or pure IL or combined solution were mixed in a conical flask. The sealed flask was shaken for 3 h in a thermostatic rotary shaker at a speed of 200 rpm at 303.2 K and then allowed to settle for no less than 3 h at the same temperature to ensure complete phase separation and thermodynamic equilibrium. Then, a sample from each phase was carefully taken with a syringe without disturbing the phase boundary. The upper phase and the bottom phase were diluted, respectively, using hexane and methanol for subsequent HPLC analysis. The extraction equilibrium experiments were repeated at least three times, and the relative uncertainties of distribution coefficients were verified within 5%.

The distribution coefficient of solute i (D_i) and selectivity of solute i over solute j ($S_{i/j}$) were calculated as

$$D_i = C_i^{ext}/C_i^{hex} \quad (1)$$

$$S_{i/j} = D_i/D_j \quad (2)$$

where C_i^{ext} and C_i^{hex} represent the concentration of solute in the extractant phase and in the hexane phase, respectively.

HPLC Analysis. To determine the exact concentrations of vitamin D_3 and tachysterol$_3$, an HPLC system equipped with a Waters 1525 pump, a Waters 717 plus autosampler, and a Waters 2487 UV detector was used. The chromatographic analysis was performed on a Waters normal-phase silica column (250 mm × 4.6 mm, 5 μm) at 308.2 K with the detection wavelength at 254 nm. The mobile phase was a mixture of hexane and pentanol (99.5:0.5, v/v) with a flow rate of 2.0 mL min^{-1}, and the injection volume was 10 μL. Prior to HPLC analysis, all samples were loaded into a syringe and passed through a membrane filter with 0.45 μm pore.

RESULTS AND DISCUSSION

Extractive Separation of Vitamin D_3 and Tachysterol$_3$ Using Organic Solvents. The extraction equilibrium of vitamin D_3 and tachysterol$_3$ in the biphasic system was performed at 303.2 K. Organic solvents including *N*-methylpyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, 1,2-propylene glycol (1,2-PDO), sulfolane, and 1,3-propylene glycol (1,3-PDO) were selected as extractants for the separation. The total initial concentration of vitamin D_3 and tachysterol$_3$ was 4.8 mg/mL, and the mass ratio of vitamin D_3 to tachysterol$_3$ was 4:1. Distribution coefficients and selectivity in all cases are presented in Table 2 and are more visually expressed in Figure 2.

As seen from Figure 2, NMP, DMF, and DMSO achieve relatively high distribution coefficients, whereas acetonitrile, 1,3-DPO, and sulfolane achieve relatively high selectivity. It is well-known that both vitamin D_3 and tachysterol$_3$ have a hydrophobic skeleton and a long hydrophobic chain. The addition of a hydroxyl group makes the molecule locally polar. According to the empirical rule "like dissolves like",[34] vitamin D_3 and tachysterol$_3$ are slightly soluble in polar solvents such as sulfolane, acetonitrile, and 1,3-DPO, thus leading to lower distribution coefficients in these solvents. On the contrary, NMP, DMF, and DMSO are generally considered to be good solvents for most chemicals due to their accessible interaction with solute molecules, so considerable distribution coefficients were obtained in the phase equilibrium experiments. As shown in Figure 1, the difference in chemical structure between vitamin D_3 and tachysterol$_3$ mainly lies in the position of double bonds. As molecules with unsaturated bonds, NMP, DMF, DMSO, acetonitrile, and sulfolane could form $\pi-\pi$ interaction with both solutes in theory, and the difference in strength of interaction between extractant and the two substances relies on the position of double bonds in their structures, thus resulting in relatively high selectivity.

Besides, it can be found that sulfolane showed optimal selectivity among the studied organic solvents. Consequently, the evolution of the distribution coefficients and selectivity of vitamin D_3 and tachysterol$_3$ for each system, as a function of the mass fraction of the solute in the hexane phase, are plotted in

Table 2. Distribution Coefficients and Selectivity of Tachysterol$_3$ to Vitamin D_3 in Hexane−Extractant Biphasic Systems at 303.2 K[a]

extractant	distribution coefficient		selectivity
	D_3	T_3	T_3/D_3
Organic Solvents			
N-methylpyrrolidone	2.032	2.682	1.32
N,*N*-dimethylformamide	1.711	2.180	1.27
dimethyl sulfoxide	0.582	0.765	1.31
acetonitrile	0.269	0.376	1.40
1,2-propylene glycol	0.220	0.261	1.18
sulfolane	0.171	0.246	1.44
1,3-propylene glycol	0.038	0.051	1.35
Ionic Liquids			
[OMIm][BF_4]	0.7372	1.0421	1.41
[HMIm][BF_4]	0.0627	0.0971	1.55
[BMIm][BF_4]	0.0074	0.0123	1.67
[BMIm][PF_6]	0.0049	0.0078	1.60
[BMIm][TfO]	0.0844	0.1402	1.66
[BMIm][NTf_2]	0.0716	0.1103	1.54
[CPMIm][NTf_2]	0.0057	0.0093	1.64
[Bpy][NTf_2]	0.0661	0.1141	1.72
[BMPr][NTf_2]	0.0597	0.1058	1.77
[EMIm][NTf_2]	0.0190	0.0277	1.46
[HOEtMim][NTf_2]	0.0077	0.0125	1.63

[a]The total initial concentration of vitamin D_3 and tachysterol$_3$ was 4.8 mg/mL, and the mass ratio of vitamin D_3 to tachysterol$_3$ was 4:1.

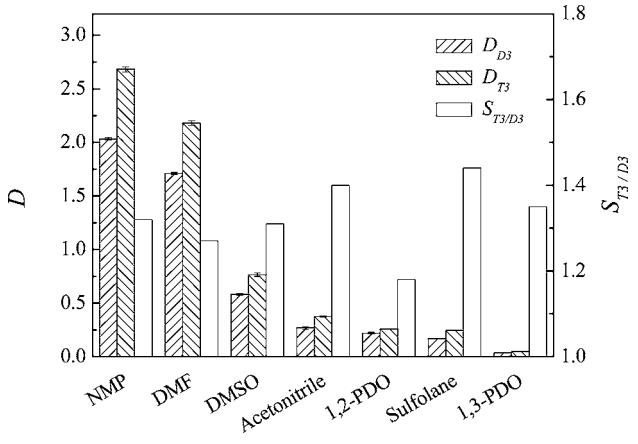

Figure 2. Distribution coefficients and selectivity of vitamin D_3 and tachysterol$_3$ in hexane−organic solvents biphasic systems at 303.2 K: (slashed bars) distribution coefficient of vitamin D_3 and tachysterol$_3$ in biphasic systems; (white bars) selectivity of tachysterol$_3$ to vitamin D_3 in biphasic systems.

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Figure 3. As the total initial concentration increased from 1 to 30 mg/mL, both distribution coefficients and selectivity of

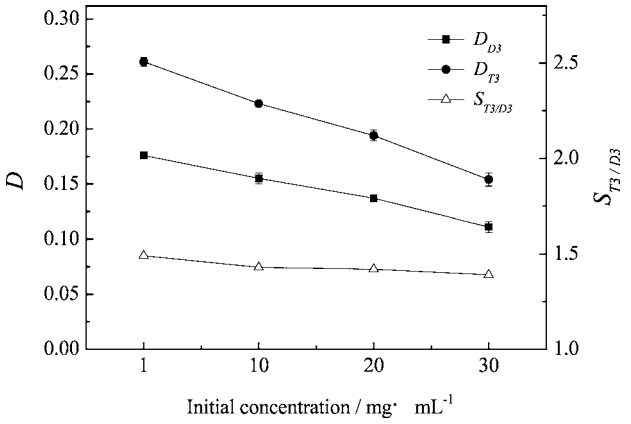

Figure 3. Distribution coefficients and selectivity of vitamin D_3 and tachysterol$_3$ in hexane−sulfolane biphasic systems at 303.2 K with different initial concentrations: (■) distribution coefficient of vitamin D_3 in biphasic systems; (●) distribution coefficient of tachysterol$_3$ in biphasic systems; (△) selectivity of tachysterol$_3$ to vitamin D_3 in biphasic systems.

vitamin D_3 and tachysterol$_3$ descend gradually. Owing to the limited solubility of vitamin D_3 and tachysterol$_3$ in sulfolane, the extra amount of solute tends to be dissolved in the hexane phase rather than sulfolane phase, thus leading to lower distribution coefficients. Therefore, a compromise between feedstock concentration and acceptable extraction performance is inevitable in a practical process.

Extractive Separation of Vitamin D_3 and Tachysterol$_3$ Using ILs. Further elevation of distribution coefficients and selectivity of tachysterol$_3$ over those of vitamin D_3 is difficult for the sake of limited optional organic solvents that could form biphasic systems with hexane. In this work, pure ionic liquids including [OMIm][BF_4], [HMIm][BF_4], [BMIm][BF_4], [BMIm][PF_6], [BMIm][TfO], [BMIm][NTf_2], [CPMIm]-[NTf_2], [BPy][NTf_2], [BMPr][NTf_2], [EMIm][NTf_2], and [HOEtMim][NTf_2] were selected as extraction solvents because of their immiscibility with hexane. The equilibrium experiments were conducted at a temperature of 303.2 K, and the results are reported in Table 2.

As was found in previously published works and our previous studies, the extraction performance is highly dependent on the type of IL anion.[31,32] $[TfO]^-$, $[NTf_2]^-$, $[BF_4]^-$, and $[PF_6]^-$ vary in polarity, size, and H-bond basicity and were selected in this work to gain insight into the interaction mechanism ascribed to the selective separation. As shown in Figure 4, when the cation was the same ($[BMIm]^+$), the distribution coefficients of vitamin D_3 and tachysterol$_3$ obtained with different anions followed the order [BMIm][TfO] > [BMIm][NTf_2] > [BMIm][BF_4] > [BMIm][PF_6]. This observed order might be attributed to the empirical rule that van der Waals interaction between two molecules increases with the increase of molecule size, so the relatively larger sizes of anions $[TfO]^-$ and $[NTf_2]^-$ result in a larger distribution coefficient of vitamin D_3 and tachysterol$_3$. In addition, [BMIm][BF_4] and [BMIm]-[PF_6] is more polar when compared to [BMIm][TfO] and [BMIm][NTf_2];[35] thus, the former ILs show weaker affinity to hydrophobic vitamin D_3 and tachysterol$_3$. Besides, the hydrogen-bonding interaction between the hydroxyl hydrogen atom

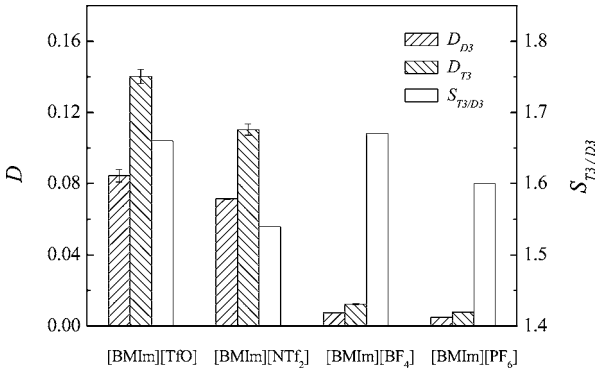

Figure 4. Effect of anion's structure of [BMIm]-based ILs on distribution coefficients and selectivity of vitamin D_3 and tachysterol$_3$ in hexane−IL biphasic systems at 303.2 K: (slashed bars) distribution coefficient of vitamin D_3 and tachysterol$_3$ in biphasic systems; (white bars) selectivity of tachysterol$_3$ to vitamin D_3 in biphasic systems.

of vitamin D_3 or tachysterol$_3$ with the oxygen atom of the sulfonyl group in $[TfO]^-$ or $[NTf_2]^-$ might be also ascribed to this observation.[36,37] The selectivity of tachysterol$_3$ to vitamin D_3 in IL [BMIm][NTf_2] and [BMIm][TfO] was found to be 1.66 and 1.54, respectively. They were 15 and 7% higher than that in sulfolane, which showed the best selectivity value among the studied organic solvents. Despite the selectivity for [BMIm][BF_4] and [BMIm][PF_6] being better, the fairly poor distribution coefficients of the studied compounds made these two ILs impractical.

Apart from anions, IL cations also have significant effects on the distribution of vitamin D_3 and tachysterol$_3$ in the biphasic systems. By modulating the side alkyl chain length in cations, IL's affinity toward solute could be greatly improved. Figure 5a provides an overall view of the influence of the side alkyl chain length in cations on distribution coefficients of vitamin D_3 and tachysterol$_3$. When the anion was the same ($[BF_4]^-$) and the side alkyl chain length in imidazole ring extended from butyl to octyl, the distribution coefficients of vitamin D_3 and tachysterol$_3$ followed an upward trend, whereas the selectivity decreased from 1.67 to 1.41, which is in accordance with the findings of Lei,[38] Pei,[39] Garcia,[40] and Hanke.[41] Recent experimental and simulation works have indicated that ionic liquids are structured fluids exhibiting segregated polar and nonpolar domains. In the case of imidazolium-based ILs, the polar domains contain the anions and the imidazolium ring of the cation, whereas the nonpolar regions are formed by the alkyl side chains of the latter. For long-chain [C_nMIm][NTf_2] ionic liquids, the hydrophobic moiety of vitamin D_3 and tachysterol$_3$ could be accommodated in the hydrophobic domain of the alkyl side chains. Accordingly, the hydrophobic interaction between ILs and the target molecule becomes stronger, and hence their solubility in the IL phase improves. It is worth mentioning that the selectivity of tachysterol$_3$ over vitamin D_3 moderately decreased as the side alkyl chain of ILs became longer.

According to previous studies, the aromatic character of ILs might enhance distribution coefficients and selectivity,[29,42] and it was also reported that the cations interact strongly with the electron-rich π systems.[43] For structural analogues that differ in the position of double bonds, cation structure seems to be vital in the determination of extracting performance. On the basis of this description, and from the molecular perspective of imidazolium-based ILs described above that polar domains

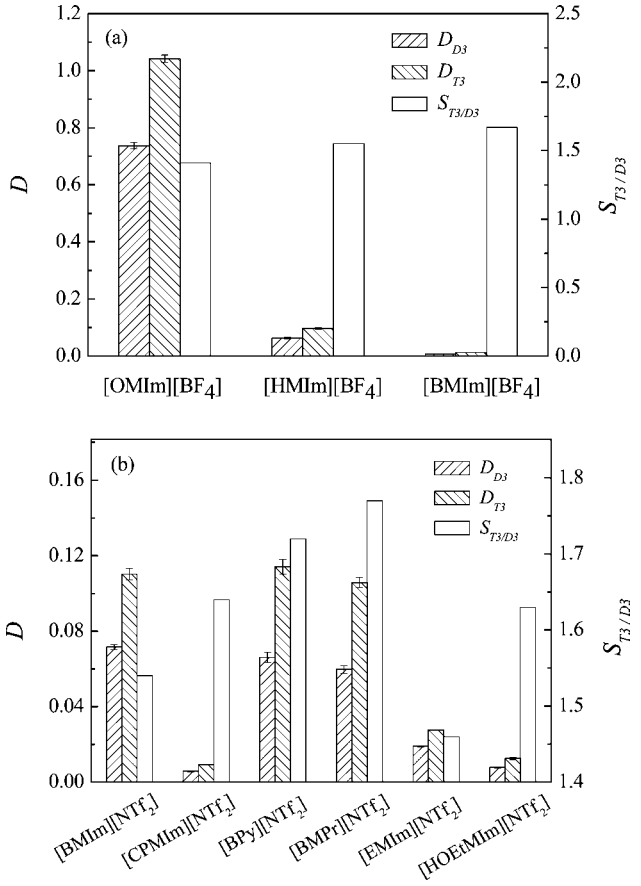

Figure 5. Effect of cation on distribution coefficients and selectivity of vitamin D_3 and tachysterol$_3$ in hexane−IL biphasic systems at 303.2 K: (slashed bars) distribution coefficient of vitamin D_3 and tachysterol$_3$ in biphasic systems; (white bars) selectivity of tachysterol$_3$ to vitamin D_3 in biphasic systems.

contain the anions and the imidazolium ring of the cation, the modulation of cation structure was expected to bring promising results. When the anion was the same ($[NTf_2]^-$), the change of the cation or the introduction of functional groups could obviously change the distribution coefficients and selectivity of vitamin D_3 and tachysterol$_3$, as seen from Figure 5b. It is noticeable that [BMPr][NTf_2] showed the largest selectivity value among all ILs, and its selectivity up to 1.77 was 23% higher than that of sulfolane. This had enhanced the extraction efficiency to a large extent. Prausnitz and Anderson's study on the mechanism for separating olefin and paraffin concluded that the interactions between extractant and the unsaturated double bond in the target molecules played a significant role in the selective extraction.[44] For ILs with a pyrrol or pyridine ring, the $\pi-\pi$ stacking interaction between target solutes and ILs is much more obvious, so the different positions of the double bonds in vitamin D_3 and tachysterol$_3$ might give rise to a more obvious difference in solubility of these two compounds, thus resulting in a higher selectivity. This result is similar to the conclusion reached by Meindersma[29] and Garcia[45] that ILs with an aromatic cation, such as pyridinium, could obtain both higher toluene distribution coefficients and higher toluene/heptane selectivity. This also implies that ILs' cation of an aromatic nature could be favorable to such a separation requirement.

As found in ILs with anion $[BF_4]^-$, [EMIm][NTf_2] had a poorer distribution coefficient than [BMIm][NTf_2] due to its short side alkyl chain in cation. When we carefully examined the extraction behavior of [BMIm][NTf_2] and [CPMIm]-[NTf_2] and of [EMIm][NTf_2] and [HOEtMim][NTf_2], it is of particular interest to note that the introduction of a functional group cyan (−CN) or hydroxyl (−OH) makes a positive contribution to the selectivity, although the distribution coefficients are sacrificed. That is because the strongly polar functional groups increase the polarity of ILs, thus reducing their affinity to hydrophobic target compounds and the intermiscibility with hexane.[46] However, with a more obvious $\pi-\pi$ interaction or polarity interaction difference among vitamin D_3 and tachysterol$_3$, the selectivity increased.

Effect of Cosolvent on the Extraction Equilibrium of Vitamin D_3 and Tachysterol$_3$. As discussed above, ILs showed higher selectivity in extractive separation of vitamin D_3 and tachysterol$_3$ compared to traditional organic solvents. However, there are also several problems with using ILs in liquid−liquid extraction particularly due to the ILs' relatively large viscosity and high cost. Consequently, mixtures of ILs and polar organic solvents were used as the extraction solvent in the study instead of pure ILs with the hope of taking advantage of both ILs and organic solvents. Meanwhile, a sound selectivity, as well as acceptable distribution coefficients, could be obtained.

As mentioned above, [BMPr][NTf_2] achieved the highest selectivity among all studied ILs. However, its affinity to vitamin D_3 and tachysterol$_3$ to some extent remained a significant limitation for its application. Therefore, we investigated the extraction performance of the combination of this IL and DMF. DMF was selected because of its relatively low viscosity, low boiling point, and great affinity with the titled compounds. Figure 6 presents the distribution coefficients and

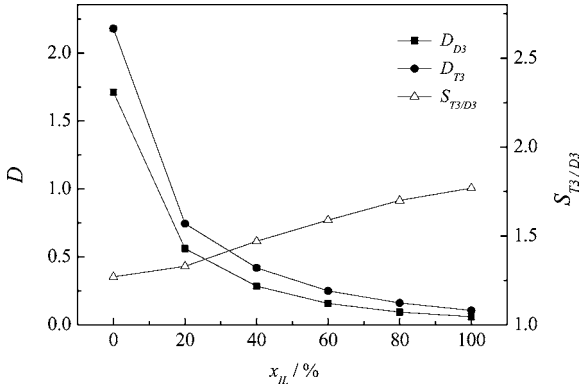

Figure 6. Effect of the initial mole fraction of [BMPr][NTf_2] in [BMPr][NTf_2]−DMF binary extraction solvent on the separation of vitamin D_3 and tachysterol$_3$: (■) distribution coefficient of vitamin D_3 in biphasic systems; (●) distribution coefficient of tachysterol$_3$ in biphasic systems; (△) selectivity of tachysterol$_3$ to vitamin D_3.

selectivity of vitamin D_3 and tachysterol$_3$ against the mole fraction of [BMPr][NTf_2] (x_{IL}) in the binary extraction solvent of [BMPr][NTf_2]−DMF. As the mole fraction of ILs increased from 0 to 100%, the distributions of vitamin D_3 and tachysterol$_3$ in the extraction phase exponentially decreased, whereas the selectivity of tachysterol$_3$ over vitamin D_3 was in a linear upward trend. When the mole fraction of [BMPr][NTf_2] was 40% in the binary [BMPr][NTf_2]−DMF extractant, the distribution coefficients of vitamin D_3 and tachysterol$_3$ were 0.285 and 0.419, respectively, and the selectivity was 1.47,

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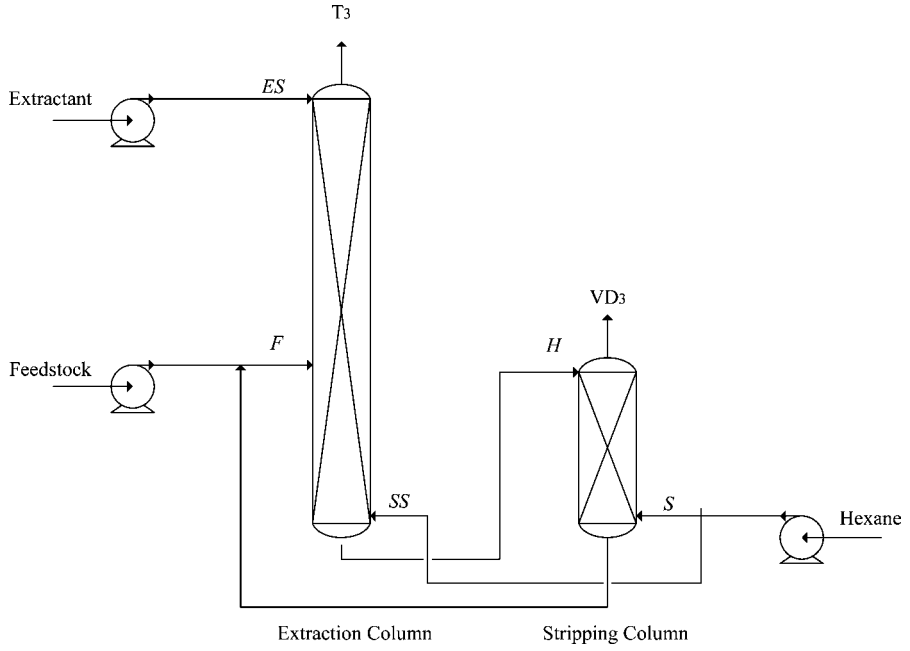

Figure 7. Flowchart of continuous multistage fractional extraction and back extraction. *ES*, *F*, and *SS* represent the flow rates of extraction solvent, feed, and scrubbing solvent in extraction column. *H* and *S* represent the flow rates of feed and stripping solvent in stripping column.

which was slightly higher compared to sulfolane, whereas the distribution coefficients doubled. When the mole fraction of [BMPr][NTf_2] increased to 60%, the distribution coefficients of vitamin D_3 and tachysterol$_3$ slightly decreased to 0.157 and 0.250, respectively, and a selectivity of 1.59 was obtained. Although similar distribution coefficients were obtained when compared with the sulfolane system, the selectivity was even 10% higher. In conclusion, mixing ILs with a kind of organic solvent is possible to gain a relatively high selectivity and a large extraction capacity as well.

Continuous Multistage Extraction. To evaluate the feasibility of the extractive process for a practical production, continuous multistage fractional extraction (flowcharts shown in Figures 7 and 8) was performed by calculations.

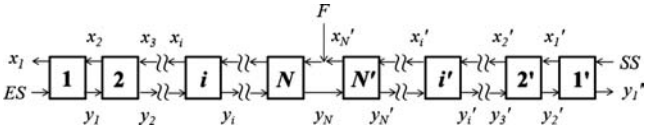

Figure 8. Flowchart of continuous multistage fractional extraction. *ES*, *F*, and *SS* represent the flow rates of extraction solvent, feed, and scrubbing solvent in extraction column. x_i and y_i represent the concentrations of vitamin D_3 and tachysterol$_3$ in stage i of the extraction column, respectively. x_i' and y_i' represent the concentrations of vitamin D_3 and tachysterol$_3$ in stage i' of the scrubbing column, respectively.

In the extraction sections

$$y_i = mx_i \tag{3}$$

$$(F + SS)x_{i+1} = ES \times y_i + (F + SS)x_1 \tag{4}$$

$$x_{i+1} = \frac{ES \times m}{F + SS} \times x_i + x_1 \tag{5}$$

where x_i and y_i represent the concentrations of vitamin D_3 and tachysterol$_3$ in stage i and *F*, *ES*, and *SS* represent the flow rates of feed, extraction solvent, and scrubbing solvent, respectively. m represents the phase equilibrium coefficient. When

$$B = \frac{ES \times m}{F + SS} \tag{6}$$

then

$$x_{i+1} = Bx_i + x_1 \tag{7}$$

$$x_N = \frac{B^N - 1}{B - 1} \times x_1 \tag{8}$$

$$y_N = mx_N = m \times \frac{B^N - 1}{B - 1} \times x_1 \tag{9}$$

In the scrubbing column

$$y_i' = mx_i' \tag{10}$$

$$ES \times y_{i+1}' = ES \times y_1' + SS \times x_i' \tag{11}$$

$$y_{i+1}' = y_1' + \frac{SS}{ES \times m} \times y_i' \tag{12}$$

where x_i' and y_i' represent the concentrations of vitamin D_3 and tachysterol$_3$ in stage i', respectively. When

$$A = \frac{SS}{ES \times m} \tag{13}$$

then

$$y_{i+1}' = y_1' + Ay_i' \tag{14}$$

$$y_{N'} = \frac{A^{N'} - 1}{A - 1} \times y_1' \tag{15}$$

according to the feed balance of the scrubbing column

$$ES \times y_N = SS \times x_N' + ES \times y_1' \tag{16}$$

and as a result

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$$y_N = \frac{SS}{ES \times m} \times y_N{}' + y_1{}' = A \times \frac{A^{N'} - 1}{A - 1} \times y_1{}' + y_1{}' = \frac{A^{N'+1} - 1}{A - 1} \times y_1{}' \quad (17)$$

when y_N is

$$y_N = m \times \frac{B^N - 1}{B - 1} \times x_1 = \frac{A^{N'+1} - 1}{A - 1} \times y_1{}' \quad (18)$$

$$y_1{}' = m \times \frac{B^N - 1}{B - 1} \times \frac{A - 1}{A^{N'+1} - 1} \times x_1 \quad (19)$$

According to the feed balance of both extraction and scrubbing columns

$$Fx_F = (F + SS)x_1 + ES \times y_1' = (F + SS)x_1 + ES \times m \times \frac{B^N - 1}{B - 1} \times \frac{A - 1}{A^{N'+1} - 1} \times x_1 \quad (20)$$

and as a result

$$x_1 = \frac{Fx_F}{F + SS + ES \times m \times \frac{B^N - 1}{B - 1} \times \frac{A - 1}{A^{N'+1} - 1}} \quad (21)$$

The result using binary [BMPr][NTf_2]−DMF as extractant with the IL concentration set at 40% is presented in Figure 9. The purity and recovery of vitamin D_3 versus the solvent-to-feed ratio $ES/(F + SS)$ (ES, F, and SS represent the flow rates of extraction solvent, feed, and scrubbing solvent, respectively) with different numbers of extraction stages (N_{ext}) are shown. When the scrubbing solvent-to-feed ratio of the scrubbing section was fixed at 0.3 and the scrubbing stage at 12, the obtained results indicated that the purity of vitamin D_3 increased and the recovery of vitamin D_3 decreased as the number of extraction stages increased. Similarly, with the increase of the solvent-to-feed ratio, the purity increased while recovery dropped. With $(ES/(F + SS))$ set at 2.5 and N_{ext} set at 16, both a purity of vitamin D_3 as high as 96% and a recovery of 88% could be obtained.

By comparing the purity of vitamin D_3 obtained using sulfolane or 40% [BMPr][NTf_2]−DMF shown in Figure 10, it is evident that IL-based liquid−liquid extraction is superior to organic solvents in all cases at a given number of stages in both extraction and scrubbing sections. At a certain $(ES/(F + SS))$, the purity of vitamin D_3 was much higher when using an IL-based extracting agent. Assuming a specific separation task asked for the purity of vitamin D_3 >98%, a far smaller $(ES/(F + SS))$ is required for the 40% [BMPr][NTf_2]−DMF binary extractant as seen from Figure 10, which means that the consumption of extracting solvent could be greatly reduced. The calculated purity of vitamin D_3 versus the number of stages of the extraction section (N_{ext}) by fractional extraction is given in Figure 11. Because a higher selectivity of tachysterol$_3$ over vitamin D_3 was obtained by 60% [BMPr][NTf_2]−DMF binary extracting agent, a reduced number of N_{ext} is necessary to realize a required purity of vitamin D_3.

The regeneration of extracting agent could be easily realized through back extraction by hexane. With the scrubbing solvent-to-feed ratio set at 2.0 and the number of stages set at 4, vitamin D_3 could be effectively eluted from the extracting agent with a recovery of >99%.

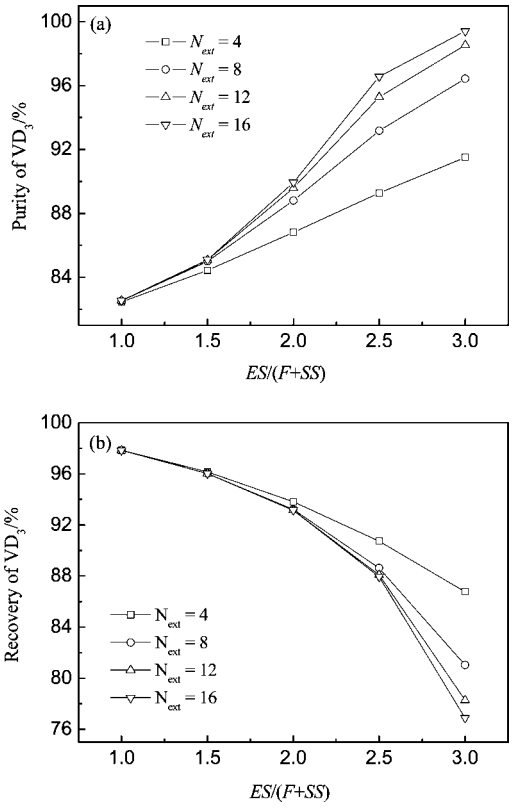

Figure 9. Calculated purity (a) and recovery (b) of vitamin D_3 versus $ES/(F + SS)$ with different N_{ext} by fractional extraction when using 40% [BMPr][NTf_2]−DMF binary solvent as extractant. The scrubbing solvent-to-extraction solvent ratio of the scrubbing section was set at 0.3. The number of stages of the scrubbing section was set at 12.

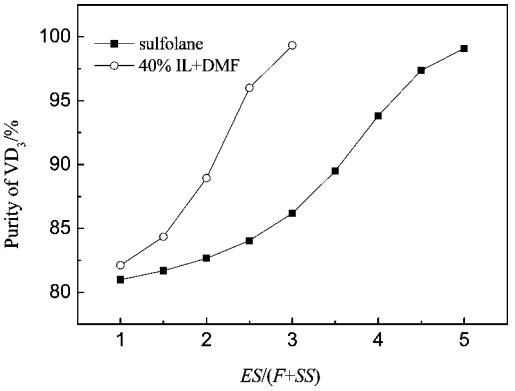

Figure 10. Calculated purity of vitamin D_3 versus $ES/(F + SS)$ by fractional extraction: (■) sulfolane; (○) 40% [BMPr][NTf_2]−DMF binary extractant. The recovery of vitamin D_3 was >88% with the number of stages of the extraction section (N_{ext}) set at 16 and the number of stages of the scrubbing section set at 12.

In conclusion, the choices of traditional biphasic extraction systems consisted of organic solvents are limited; as a result, satisfactory extraction performance is generally unavailable for the separation of structural analogues. In this work we attempted to use ILs as extrantant to separate vitamin D_3 and tachysterol$_3$ that differ only in the position of double bonds in their chemical structures. The selective separation of vitamin

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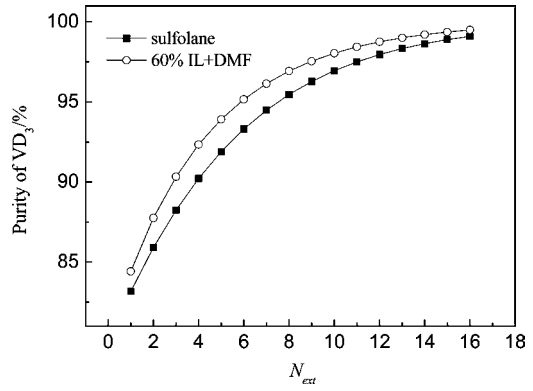

Figure 11. Calculated purity of vitamin D_3 versus the number of stages of the extraction section (N_{ext}) by fractional extraction: (■) sulfolane; (○) 60% [BMPr][NTf_2]−DMF binary extractant. $ES/(F + SS)$ was set at 5.0, and the number of stages of the scrubbing section was set at 12.

D_3 and tachysterol$_3$ by solvent extraction with 7 organic solvents and 11 ILs was reported, and an insight on how the modification of anion and cation of ILs influenced the extractive performance was provided. A conclusion was drawn that ILs with unsaturated bonds obtained higher selectivity due to their more obvious $\pi-\pi$ interaction difference between these two compounds. When the anion of the ILs were $[TfO]^-$ or $[NTf_2]^-$, or the cation of the ILs included a pyridine ring or pyrrole ring, the studied solutes had a sound distribution in IL phase, and the selectivity was also relatively acceptable. The introduction of a −CN or −OH functional group in the alkyl chain increased the polarity of ILs, thus giving rise to the selectivity and decreasing distribution coefficient. Furthermore, good selectivity and distribution coefficients were observed by a combination of organic solvents and ILs as extracting agents. Finally, a comparison was also made by calculating the purity and recovery of vitamin D_3 when respectively using ILs and organic solvent in continuous multistage extractions, which revealed that IL-based liquid−liquid extraction was superior to organic solvents in practical production.

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Notes

The authors declare no competing financial interest.

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