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Equilibrium partitioning of drug molecules between aqueous and amino acid ester-based ionic liquids

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ABSTRACT

In this work, a series of novel room temperature ionic liquids (ILs) have been synthesized with cheap, naturally α-amino acid ester as cations and bis(trifluoromethylsulfonyl)imide as anion. The glass transition temperature and thermal decomposition temperature of these ILs, partition coefficients of some coumarins and purine alkaloids between water and the amino acid ester-based ILs at $T = 298.15$ K, and Gibbs energy, enthalpy and entropy changes for the transfer of caffeine and 6,7-dihydroxycoumarin from water to [$LeuC_2$][Tf_2N] have been determined. It is shown that these ILs are highly effective materials for the extraction of drug compounds like coumarin, 4-hydroxycoumarin, 7-hydroxycoumarin, 3-aminocoumarin, coumarin-3-carboxylic acid, 6,7-dihydroxycoumarin, 6,7-dihydroxy-4-methylcoumarin, caffeine, theobromine, theophylline, inosine, and 2,6-diaminopurine. The partition process is driven by enthalpy term, and partition coefficients of the drug molecules increase with the increase of hydrophobicity of both the drug molecules and the ILs. Furthermore, the possible partition mechanism has been investigated from ^{13}C NMR measurements.

1. Introduction

Coumarins are often found naturally in some plants [1,2], and used as food additive, drugs and ingredient in perfume because of their distinctive odor. They have the functions of anti-HIV, anti-tumor, anti-hypertension and among others [1]. Purine alkaloids, such as caffeine, theobromine and theophylline, are usually extracted in varying quantities from seeds, leaves and fruits of some plants, and applied as vasodilator, diuretic and heart stimulant medicines [3]. The extraction/isolation of these compounds is the premise of their use. However, in the traditional extraction/isolation process of coumarins and purine alkaloids, a large number of volatile organic solvents have to be used [1–4], which may cause environmental problems. In order to make the process to be greener, new systems must be developed.

As an innovative class of solvents, ILs have a variety of unique properties, such as negligible vapor pressure, non-flammability, high thermal and chemical stability, tunable structures and properties, and strong solubilization power [5–7]. This makes them as a potential replacement for volatile organic solvents used in chemical synthesis, biocatalytic transformation, electrochemistry, carbon dioxide absorption, nanomaterials preparation, cellulose dissolution, light-emitting materials and among others [5–10].

In addition to the above versatile applications, ILs have been used, in recent years, as "green" solvents to extract a variety of substances [8,11–14]. However, the research and development of ILs are still in their infant stage, there are many problems to be explored. For example, the ILs used for extraction process are mainly imidazole- or pyridine-based salts, which are still expensive and become one of the main bottlenecks for the industrialization of ILs. Moreover, imidazole- or pyridine-based ILs are poorly biodegradable [15–17]. This is another problem for their industrial application. Thus, development of novel ILs with cheap biomaterials and easy synthesis route is very imperative. In this context, the "green" feature of ILs can be greatly improved [18–21], and their price may be significantly reduced.

In this work, a series of novel room temperature ILs have been synthesized from cheap, naturally α-amino acid ester by a simple procedure, and characterized by ^1H NMR, glass transition temperature and thermal decomposition temperature. Partition coefficients of some coumarins and purine alkaloids between water and the amino acid ester-based ILs have been determined at $T = 298.15$ K to evaluate the structural effects of the ILs and the drug molecules. In order to understand the partitioning of the drug molecules in these ILs from a point of view of thermodynamics, Gibbs energy, enthalpy and entropy changes for the transfer of caffeine and 6,7-dihydroxycoumarin from water to [$LeuC_2$][Tf_2N] have also been measured. Meanwhile, the possible partitioning mechanism has been investigated from ^{13}C NMR measurements.

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2. Experimental section

2.1. Materials

$LiTf_2N$ (>99%) was purchased from Zhejiang Jiuzhou Pharmaceutical Co.; leucine methyl ester hydrochloride (>98%), leucine ethyl ester hydrochloride (>98%), phenylalanine methyl ester hydrochloride (>98%), phenylalanine ethyl ester hydrochloride (>98%), tryptophan ethyl ester hydrochloride (>98%), phenylglycine methyl ester hydrochloride (>98%), glycine benzyl ester hydrochloride (>98%), coumarin (>99%), 7-hydroxycoumarin (>99%), caffeine (>98%), theobromine (>98%), theophylline (>98%), inosine (>98%), and 2,6-diaminopurine (>98%) were purchased from Shanghai Aladdin-reagent Co.. Coumarin-3-carboxylic acid (>98%), 4-hydroxycoumarin (>98%), 3-aminocoumarin (>98%), 6,7-dihydroxycoumarin (>98%), 6,7-dihydroxy-4-methylcoumarin (>97%) were purchased from Alfa-aesar. These Chemicals were used without further purification. Double distilled water was used throughout the experiments.

2.2. Synthesis of the amino acid ester-based ILs

Briefly, the reactions of $Li[Tf_2N]$ with any amino acid ester hydrochlorides (leucine methyl ester hydrochloride, leucine ethyl ester hydrochloride, phenylalanine methyl ester hydrochloride, phenylalanine ethyl ester hydrochloride, tryptophan ethyl ester hydrochloride, phenylglycine methyl ester hydrochloride, and glycine benzyl ester hydrochloride) were carried out in water at room temperature with stirring for 12 h. After the reactions, the IL phase was collected, and washed by water until no precipitation of AgCl can be found by addition of a few drops of aqueous $AgNO_3$. Then, the residual water was removed by rotary evaporation, and the resulting products were dried under vacuum for 36 h. The structures of the ILs investigated in this work were depicted in figure 1.

2.3. Characterization of the ILs

All the purified ILs were characterized by ^1H NMR (Bruker, AV-400) spectroscopy at 298.15 K to confirm the absence of any major impurities, and the purity of these ILs is found to be greater than 99% in mass fraction. The ^1H NMR data are reported as follows.

TABLE 1
The initial concentrations and the maximum absorption wavelength (λ_{max}) of the drug compounds.

Drug	Initial concentration/g · L^{-1}	λ_{max}/nm
Coumarin	0.544	272
4-Hydroxycoumarin	0.112	302
7-Hydroxycoumarin	0.104	323
3-Aminocoumarin	0.124	323
Coumarin-3-carboxylic acid	0.124	310
6,7-Dihydroxycoumarin	0.120	323
6,7-Dihydroxy-4-methylcoumarin	0.092	323
Caffeine	1.008	274
Theobromine	0.464	274
Theophylline	1.048	274
Inosine	1.024	274
2,6-Diaminopurine	1.040	274

TABLE 2
Thermal decomposition temperature and glass transition temperature of the ILs.

IL	T_g/K	T_d/K
$[LeuC_1][Tf_2N]$	230.4	560.2
$[LeuC_2][Tf_2N]$	229.3	554.0
$[PheC_1][Tf_2N]$	254.1	578.4
$[PheC_2][Tf_2N]$	240.3	559.4
$[GlyOBzl][Tf_2N]$	247.6	589.6
$[Gly(Phe)C_1][Tf_2N]$	261.4	577.2
$[TrpC_2][Tf_2N]$	260.2	541.2

$[LeuC_1][Tf_2N]$: ^1H NMR (400 MHz, $[D_6]$ DMSO, TMS): δ = 0.95 (d, 6H, CH_3), 1.65 to 1.80 (m, 3H, CH_2, CH), 3.79 (s, 3H, CH_3), 4.08 (t, 1H, CH), 8.25 (s, 3H, NH_3) ppm.

$[LeuC_2][Tf_2N]$: ^1H NMR (400 MHz, $[D_6]$ DMSO, TMS): δ = 0.95 (d, 6H, CH_3), 1.26 (t, 3H, CH_3), 1.53 to 1.80 (m, 3H, CH_2, CH), 4.02 (t, 1H, CH), 4.20 (q, 2H, CH_2), 8.25 (s, 3H, NH_3) ppm.

$[PheC_1][Tf_2N]$: ^1H NMR (400 MHz, $[D_6]$ DMSO, TMS): δ = 3.08 (m, 2H, CH_2), 3.70 (s, 3H, CH_3), 4.37 (t, 1H, CH), 7.22 (m, 5H, benzene ring H), 8.28 (s, 3H, NH_3) ppm.

$[PheC_2][Tf_2N]$: ^1H NMR (400 MHz, $[D_6]$ DMSO, TMS): δ = 1.08 (t, 3H, CH_3), 2.98 to 3.20 (m, 2H, CH_2), 4.10 (q, 2H, CH_2), 4.30 (t, 1H, CH), 7.28 (m, 5H, benzene ring H), 8.29 (s, 3H, NH_3) ppm.

$[GlyOBzl][Tf_2N]$: ^1H NMR (400 MHz, $[D_6]$ DMSO, TMS): δ = 3.90 (s, 2H, CH_2), 5.22 (s, 2H, CH_2), 7.40 (m, 5H, benzene ring H), 8.22 (s, 3H, NH_3) ppm.

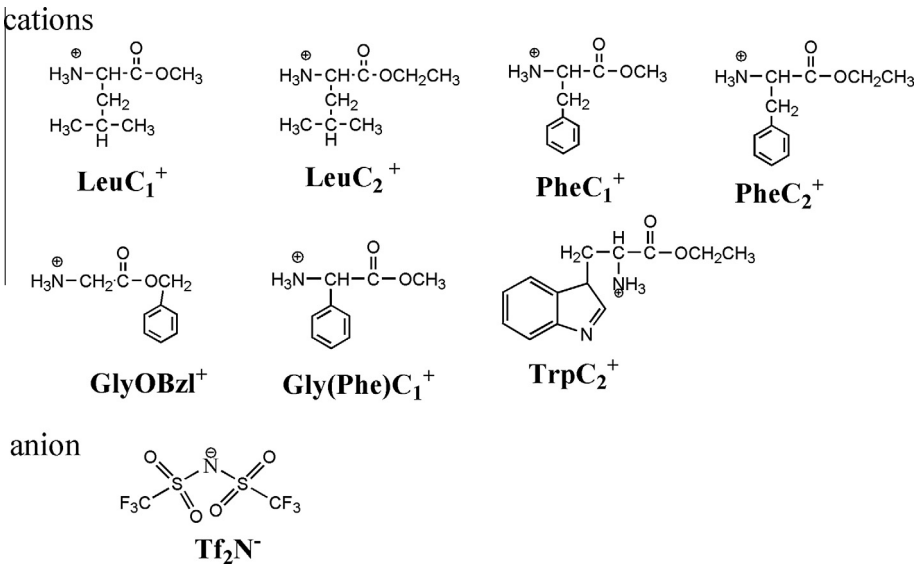

FIGURE 1. Structure of the ILs investigated.