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Extraction of Nitrofurantoin Using Ionic Liquids

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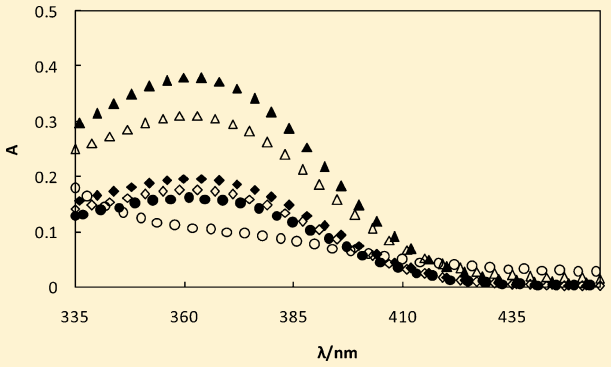
Supporting Information

ABSTRACT: Imidazolium ionic liquids have been studied as the pH−composition dependent liquid−liquid extraction processes of nitrofurantoin (NIT) in binary mixtures composed of the ionic liquid (IL) 1-hexyloxymethyl-3-methylimidazolium tetrafluoroborate, $[C_6H_{13}OCH_2MIM][BF_4]$, or 1,3-dihexyloxymethylimidazolium bis{(trifluoromethyl)sulfonyl}imide, $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ and water at a temperature of 298.15 K and at ambient pressure. The determination of the partition coefficients between the IL and aqueous solution was made. The ternary system of {IL (1) + NIT (2) + water (3)} was studied to analyze the performance of the IL in the selectivity of extraction of NIT from aqueous medium. It was found that the distribution coefficients of NIT were strongly dependent on the pH of the aqueous phase. The experimental results were discussed in a frame of the molecular interactions and the influence of the type of cation and anion of the IL. The densities of two ILs were determined as a function of temperature on a range of temperature, (298.15 to 348.15) K.



INTRODUCTION

The separation of biomolecules, amino acids, proteins, carbohydrates, alkaloids, polysaccharides, or tannins from plant materials or from natural sources is an essential task in new biotechnological processing.[1−7] Since ionic liquids (ILs) are unique solvents with special solvation properties, they are under intensive investigation, especially in separation and extraction.[1−7] The specific properties of ILs, that is, high selectivity in the separation of aromatic hydrocarbons, or thiophene from aliphatic hydrocarbons, or separation of ethanol from the azeotropic mixture with *n*-heptane, makes ILs interesting for new technologies. Recently, the hydrophilic ILs were used in the aqueous biphasic system (ABS) for the separation and purification of vital biomolecules, L-tryptophan, *β*-carotene, rhodamine 6G, and caffeine.[1] Opposite, the hydrophobic ILs were proposed as alternatives to volatile organic solvents in the liquid−liquid extraction of aminoacid L-tryptophan, as a model biomolecule from the aqueous medium.[2] The opportunity of using different inorganic salts (K_3PO_4, Na_2SO_4) is of significance due to the possible ion exchange between the salt and the IL which results in a different IL forming in the solution.[1,8] The ABS of 1-butyl-3-methylimidazolium chloride, [BMIM][Cl], was used in fine-tuning separation of glycine, L-serine, and L-proline.[8] ABS's composed of two immiscible phases, both of which are water-rich phases in the presence of aminoacids, have been intensely explored for the recovery of drug molecules and antibiotics.[9]

Different ILs as entrainers were used in bioextraction, for example, imidazolium-based chlorides or methylsulfates, phosphonium bromide, tosylate,[1] imidazolium-based, pyrrolidinium-based, pyridinium-based, or piperidinium-based bis{(trifluoromethyl)sulfonyl}imides, hexafluorophosphates, or tetrafluoroborates,[2] imidazolium-based triflate,[5] or imidazolium-based alkylphosphonate.[6]

The current study focuses on the use of 1-hexyloxymethyl-3-methylimidazolium tetrafluoroborate, $[C_6H_{13}OCH_2MIM][BF_4]$, and 1,3-dihexyloxymethylimidazolium {bis(trifluoromethyl)sulfonyl}imide, $[(C_6H_{13}OCH_2)_2IM][NTf_2]$. The chemical structures are presented in Figure 1.

The phase equilibrium, liquid/solid−liquid (LLE or SLE), of these ILs with some popular organic solvents and water were measured by us earlier.[10,11] The typical immiscibility in the liquid phase with an upper critical solution temperature (UCST) or complete solubility of the IL at room temperature in many solvents was presented. As for many ILs, the choice of anion was shown to have large impact on the solubility in molecular organic solvents: by changing the anion $[NTf_2]^-$ to $[BF_4]^-$, the solubility in hydrocarbons and alcohols decreased. When the methyl group was changed with the second alkoxy-group on the imidazolium ring, the hydrogen bonding and the other specific interactions with polar solvents increase, and

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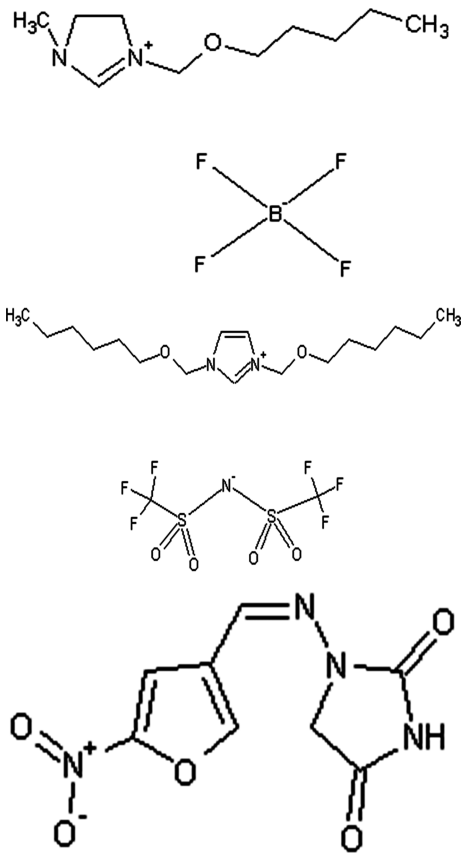

Figure 1. Chemical structure of the two used ILs, $[C_6H_{13}OCH_2MIM][BF_4]$ and $[(C_6H_{13}OCH_2)_2IM][NTf_2]$, and nitrofurantoin (NIT).

automatically the solubility in polar solvents increases.[12] Thus this paper follows the discussion on alkoxy-imidazolium ILs and is a continuation of our systematic study on the possible application in the ABS extraction of pharmaceuticals. The number of alkoxy-groups (e.g., one group in 1-hexyloxymethyl-3-methylimidazolium cation, $[C_6H_{13}OCH_2MIM]^+$ or two groups in 1,3-dihexyloxymethylimidazolium cation, $[(C_6H_{13}OCH_2)_2IM]^+$, as well as of the different anions $[BF_4]^-$ or $[NTf_2]^-$) was shown already.[12] The imidazolium-based ILs with the alkoxymethyl-groups as a substituents are known as the substances with antimicrobial activities[13] or wood preservatives.[14,15] These substituents at the imidazolium ring were shown to have influence on the high solubility of aromatic hydrocarbons in the ILs.[10]

The goal of this work is to assess the suitability of $[C_6H_{13}OCH_2MIM][BF_4]$, and $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ for use in solvent-enhanced separation processes. The solvation of drug molecule in the ILs and aqueous phase and the separation process in the IL will be discussed. The partition coefficients were developed at T = 298.15 K. The pH dependence of the partition coefficients was evaluated. The data obtained were analyzed to determine the influence of the IL anion and cation in comparison with other ILs.

In this paper nitrofurantoin (NIT) was investigated (molecular mass, 238.16 g·mol^{-1}; the molecular structure is presented in Figure 1) as a model compound of antibiotics. The recovery of aminoacids, antibiotics, and other biomolecules from natural sources and aqueous media is an important task in biotechnology.[2] NIT is a well-known antibacterial drug used in the treatment of different infections. NIT is poorly soluble in water (190 mg·dm^{-3} at T = 310 K).[16,17] It was shown by us in our previous paper that NIT is better soluble in alcohols as 1-octanol and ethanol (mole fraction $x = 6\cdot10^{-6}$ in water, $x = 3\cdot10^{-5}$ in ethanol, and $x = 7\cdot10^{-5}$ in 1-octanol at T = 298.1 K).[18]

EXPERIMENTAL SECTION

Materials. NIT (CAS Registry No. 67-20-9) was purchased from Sigma-Aldrich (St. Louis, MO, USA). This drug reveals high hydrophobicity and possible different interactions with polar solvents.

The synthesis of 1-hexyloxymethyl-3-methylimidazolium tetrafluoroborate and 1,3-dihexyloxymethylimidazolium bis-{(trifluoromethyl)sulfonyl}imide was described by Pernak and co-workers earlier.[13−15] The purification and characterization by the ^{1}H NMR and ^{13}C NMR spectra (Varian model XL 300 spectrometer) were presented earlier.[13−15] The purity of the ILs in mass fraction was > 0.999.

Water used in this study was twice distilled, degassed, deionized, and filtered with Millipore Elix 3. Hydrochloric acid (POCh, Gliwice, 1 mol aqueous solution) was used to adjust the pH of the saturated solution of NIT. 2-Propanol used for the calibration curve of NIT was purchased from Sigma Aldrich Chemie GmbH (Steinheim, Germany, for HPLC, ≥ 99.8 mass %,GC).

Water Content. The Karl Fischer titration technique (method TitroLine KF) was used for the water control. The water content was less than 268 ppm and 302 ppm for $[C_6H_{13}OCH_2MIM][BF_4]$ and $[(C_6H_{13}OCH_2)_2IM][NTf_2]$, respectively. The error is ± 10 ppm for the 3 mL injected IL.

Density Measurements. The Anton Paar GmbH 4500 vibrating-tube densitometer was used for the density measurements. The apparatus was thermostatted in a range of temperatures from (298.15 to 348.15) K. The temperature control internally was in a range of T ± 0.01 K. The precision of the measurements is $1\cdot10^{-5}$ g·cm^{-3}. The uncertainty of the measurements is ± $1\cdot10^{-4}$ g·cm^{-3}. The densities of ILs as a function of temperature are listed in Table 1 together with the linear correlation polynomial.

Table 1. Experimental Densities, ρ, of Pure Substances, $[C_6H_{13}OCH_2MIM][BF_4]$ and $[(C_6H_{13}OCH_2)_2IM][NTf_2]$[a]

ρ/(g·cm^{-3})					
T/K = 298.15	308.15	318.15	328.15	338.15	348.15
$[C_6H_{13}OCH_2MIM][BF_4]$[b]					
1.1531	1.1458	1.1387	1.1316	1.1246	1.1176
$[(C_6H_{13}OCH_2)_2IM][NTf_2]$[c]					
1.2549	1.2461	1.2373	1.2285	1.2197	1.2109

[a]The standard uncertainty is $u(\rho)$ < 0.0001. [b]ρ/(g·cm^{-3}) = $-7.0771\cdot10^{-4}T$/K + 1.3639; R^2 = $9.9997\cdot10^{-1}$. [c]ρ/(g·cm^{-3}) = $-8.8000\cdot10^{-4}T$/K + 1.5173; R^2 = 1.0000.

Biphasic Liquid−Liquid Measurements. UV−vis spectroscopy was applied to determine the concentration of NIT in the water-rich liquid phase (upper phase) that coexists with an IL-rich phase. From these data the IL−water partition coefficients of NIT were determined at one temperature, 298.15 K, and atmospheric pressure as a function of pH. Aqueous solutions of NIT of different concentrations were prepared. 2-Propanol was added to all solutions in the proportion 3:1, and samples were stirred (200 rpm) for a

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minimum of 24 h. After the next 12 h the calibration curve for NIT in water was made using a UV−vis spectrophotometer (PerkinElmer Life and Analytical Sciences, Shelton, CT, USA). The reference cuvette was filled with the 2-propanol. The overall experimental uncertainty for the temperature was estimated to be ± 0.05 K. Photometric accuracy (NIST 930D Filter 1A) obtainable with UV−vis spectrophotometer is ± 0.001 A and repeatability ≤ 0.001 A. The uncertainty in composition was $1 \cdot 10^{-6}$ mol·dm^{-3}. Many series of UV spectra were recorded at T = 298.15 K, and for each sample the obtained peaks were analyzed. The calibration curve for the chosen wavelength λ = 370 nm is shown in Figures 1S and 2S in the Supporting Information (SI).

Aqueous saturated solutions of two ILs were prepared (after stirring, 300 rpm at 298.15 K for 24 h), and solutions of different pH were obtained after the addition of HCl. After the next 24 h the stabilized pH was measured with a pH/conductivity-meter (product CPC-401 ELMETRON) with an associated uncertainty of ± 0.01. These solutions were used to prepare solutions of different concentrations of NIT. Next, the sample of NIT aqueous solution was taken with a syringe from the water-rich phase (about 5 mL) and was mixed with 2 mL of the pure IL. The masses of both samples were determined by a balance (Mettler Toledo AE 240). The mixture was placed in a thermostatted vessel with stirring (300 rpm) for the next 24 h. This was a minimum time required for the extraction processes to be completed at T = 298.15 K and was established in preliminary tests. Mixtures were thermostatted in the temperature-controlled thermostat (Lauda A 3, Germany) through the jacket of the vessel with stirring. Next, about 20 mL of a biphasic mixture (containing about $3 \cdot 10^{-6}$ mol·dm^{-3} of NIT) was taken for an analysis. After equilibration and phase separation, a sample (1.5 mL) was taken with a syringe from the water-rich phase and was mixed with a known amount of 2-propanol, 1:3. Again, the masses of both the sample and the diluent were determined by a balance (Mettler Toledo AE 240). A quartz cuvette (path length 10 mm) was filled with the diluted 2-propanol solution of the IL and the UV spectrum was recorded between (330 and 430) nm. In this sensitive region, absorbances (A) were dependent on the pH of the solution, and these are shown in Figures 2 and 3. The corresponding drug concentration in the IL-rich phase was calculated by mass balance. After the previous work in the same field it was assumed that only drug was transferred from one phase to another since the aqueous phase was saturated by the IL before the partition experiment.[2]

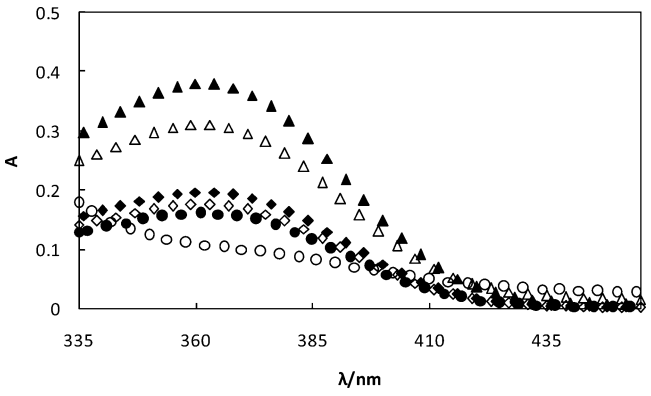

Figure 2. Dependence of absorbance on the wavelength for NIT and $[C_6H_{13}OCH_2MIM][BF_4]$ at T = 298.15 K (at pH: ▲, 1.28; △, 1.30; ◆, 1.78; ◇, 1.84; ●, 1.99; ○, 2.66).

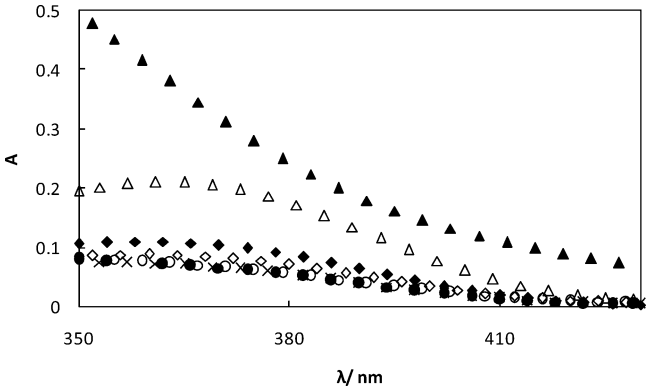

Figure 3. Dependence of absorbance on the wavelength for NIT and $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ at T = 298.15 K (at pH: ▲, 1.89; △, 2.04; ◆, 2.57; ◇, 3.63; ●, 4.23; ○, 4.56; ×, 6.46).

The flow diagram of the experiment proceeded in the steps: (1) preparation of saturated solution of each IL in water; (2) spectrophotometric measurements of the calibration curve for aqueous solutions of NIT of different concentrations and pH = 7 with 2-propanol; (3) preparation of saturated aqueous solutions of each IL and different pH (addition of HCl); (4) stirring for 24 h at constant temperature, T = 298.15 K; (5) measurements of pH after the next 24 h for stabilized solutions; (6) preparation of mixtures with NIT, thermostatted and vigorously stirred 24 h; (7) spectrophotometric measurements of the NIT concentration in the aqueous phase as a function of pH.

RESULTS AND DISCUSSION

Table 2 shows the average partition coefficients of NIT between the IL and the water-rich phase, $P_{IL/W}$ and $P^*_{IL/W}$,

Table 2. Partition Coefficients, $P_{IL/W}$ and $P^*_{IL/W}$, of NIT between the IL and the Water-Rich Phase as a Function of the pH at T = 298.15 K and p = 101.33 kPa[a]

pH	$P_{IL/W}$	$P^*_{IL/W}$
	$[C_6H_{13}OCH_2MIM][BF_4]$	
1.30	8.8	7.6
1.48	5.8	5.0
1.99	3.4	2.9
2.14	2.94	2.54
2.28	2.37	2.05
2.66	1.53	1.32
3.13	0.48	0.41
3.46	0.49	0.43
	$[(C_6H_{13}OCH_2)_2IM][NTf_2]$	
1.89	19.7	15.9
2.04	16.7	13.5
2.57	13.0	10.5
3.63	7.9	6.4
4.23	6.8	5.5
4.56	6.0	4.9
6.46	2.05	1.65

[a]Standard uncertainties are: $u(p)$ = ± 0.03 kPa, $u(P_{IL/W})$ < 3 %, $u(T)$ = 0.05 K.

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values at temperature T = 298.15 K as a function of pH for two used ILs, which were calculated from eqs 1 and 2, respectively:

$$P_{IL/W} = c_{IL}/c_W \quad (1)$$

$$P^*_{IL/W} = m_{IL}/m_W \quad (2)$$

where $P^*_{IL/W}$ is a partition coefficient described by mass, c is the molar concentration /(mol·dm^{-3}), m is mass of NIT/(g·g^{-1}), and IL and W means IL and water, respectively. Data presented in Table 2 are the average of three experiments measured with the uncertainty lower than 3 %.

All pharmaceutical companies are interested in the pH−solubility characteristics of drugs. The calculations of pH−solubility profiles for pharmaceuticals with different substituents, which is important for the improved structure of drugs for the specific therapeutic applications, have improved over the past decade.[19] The pK_a values showing the ionization of the molecule are very important and are dependent on the buffer used. The pH−solubility profile, which is usually Z-shaped, depends on the buffer used also because of the salting in/out effects and common ion effects.[20] It is well-known that the drug molecule can be present in solution in different forms due to the ionization/protonation of the polar groups (for NIT these are C═O, NH, NO_2, nitrogen, and oxygen atoms in the molecule). The protonation constant value developed by us earlier is pK_a = 6.67 (pH = 7.0).[18] In this work, the pH has a deep influence on the NIT distribution between the IL and the water-rich phase (see Table 2). However, all data are at pH values below the pK_a value, and NIT is present in the unionized form in the solution. The interaction of NIT with the IL becomes different in nature and smaller in magnitude in this area of pH.

The experimental data exhibit higher values of $P_{IL/W}$ for $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ than for $[C_6H_{13}OCH_2MIM][BF_4]$, which can be explained by the higher solubility of NIT in the former IL. Also a smaller amount of $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ is present in the water phase (less interaction with NIT) because the solubility of $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ in water is lower than that of $[C_6H_{13}OCH_2MIM][BF_4]$. The values of $P_{IL/W}$ for the IL with the $[BF_4]^-$ anion, $[C_6H_{13}OCH_2MIM][BF_4]$, are even lower than 1, $P_{IL/W}$ < 1.5, for pH higher than 2.66. All values of $P_{IL/W}$ for $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ are higher than 1, $P_{IL/W}$ > 1, which is evidence of more advantageous interaction of NIT with the IL. The interaction of the IL with drug is coming from the availability of localized or delocalized π electron clouds, lone pair electrons, permanent dipoles enhancing the affinity of the IL for organic substances, and Coloumbic and electrostatic interactions with the IL. It can be observed from the hierarchy that increasing the number of alkoxy-groups and the change of anion for $[NTf_2]^-$ are favorable for increasing the solubility of NIT. It was observed by us earlier that two alkoxy-groups in the imidazolium-based ILs increases the solubility of aromatic hydrocarbons in the IL.[11] Thus the IL with the $[NTf_2]^-$ anion and more "hydrophobic" cation with two long alkyl chains improves the extraction process. However, we do not present two ILs with the same cation and anion among both ILs; the choice of the IL has a large impact on the $P_{IL/W}$ of the system. It is widely known that the solubility of pharmaceuticals increases in the ILs in comparison with water, as for example the solubility of ibuprofen in 1-butyl-3-methylimidazolium hexafluorophosphate, $[BMIM][PF_6]$ or in 1-hexyl-3-methylimidazolium hexafluorophosphate, $[HMIM][PF_6]$.[21]

The systematic increase of the pH decreases the $P_{IL/W}$ values for both ILs. It was also observed for different aminoacids in many different ILs.[2] All values measured here are higher than for simple dialkylimidazolium-based ILs and different amino acids. Only for L-tryptophan in $[C_6MIM][BF_4]$ at pH = 1.01 the value is similar, 7.8.[2] Both use the same anion and the same length of the alkyl chain at the imidazolium cation.

The comparison of the $P_{IL/W}$ values in two used ILs is not surprising. The $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ shows not only better distribution between the IL and the aqueous phase but represents also a more stable IL. From practical point of view, the use of tetrafluoroborate-based ILs for the extraction of drugs or other biomolecules from aqueous phase is not recommended because they are not stable in the presence of water. A very slow hydrolysis of the $[BF_4]^-$ anion is sometimes known to occur in water.[22,23]

The separation of NIT in the IL/water system has to our knowledge never been measured for these and other ILs. It was concluded that, under the studied conditions, the system always contain two liquid phases and that the distribution of NIT shows a beneficial behavior for liquid−liquid extraction. The effectiveness of using $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ IL should be very high after two cycles. After the extraction process, drugs can be separated from the IL by the freezing procedure, or the IL can be dissolved in salted water (different pH's), or in cyclohexane (good solvent for $[(C_6H_{13}OCH_2)_2IM][NTf_2]$).

CONCLUSIONS

This research examined the partition coefficients for NIT in water/IL systems for two ILs. The feasibility of using the IL as a solvent to perform the extraction of NIT from a mixture with water was evaluated as a function of pH at T = 298.15 K. The results indicate that high extraction of NIT from the aqueous phase with $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ IL can be expected and the results can be extrapolated to other drugs of interest. It was showed earlier that the use of $[NTf_2]^-$ anion in biocatalytic process reveals much better results of extraction than the $[BF_4]^-$ anion. Additionally, it can be assumed from the earlier solubility measurements that the dihexyloxymethylimidazolium cation increases the partition coefficient in comparison to dialkyl-imidazolium-based ILs.[11]

The $P_{IL/W}$ of NIT with $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ IL measured here were close to 20 at low pH, being higher than for many separation processes described in the literature. This is a result of interaction of two alkoxymethyl-groups with NIT. However, the toxicity of $[(C_6H_{13}OCH_2)_2IM][NTf_2]$ IL is not known, and the antibacterial properties of that IL are not supposed to disturb the antibacterial treatment of NIT. In the future work the extraction with nonfunctionalized and similar imidazolium-based IL is planned to measure to compare the results of NIT extraction.

ASSOCIATED CONTENT

Supporting Information

Calibration curve for NIT (Figure 1S) and corresponding spectra (Figure 2S). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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