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Enhancing Artemisinin Solubility in Aqueous Solutions: Searching for Hydrotropes based on Ionic Liquids

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ABSTRACT

Artemisinin is a sesquiterpenoid lactone peroxide, known for its potent antimalarial activity that can be extracted from *Artemisia annua L.* This compound is only sparingly soluble in water, making its extraction using environmental-friendly and non-toxic aqueous solvents difficult. In the attempt to overcome this limitation, hydrotropes, which are a class of compounds that can assist in increasing the solubility of hydrophobic solutes in water, were investigated in this work. In particular, the hydrotropic capability of ionic liquids (ILs) on the aqueous solubility of artemisinin was studied. The effects of IL concentration and anion nature of 1-butyl-3-methylimidazolium-based ILs on the solubility of artemisinin at 303.2 K in water were evaluated. It is here shown the excellent capacity of ILs containing thiocyanate or dicyanamide anions to enhance the solubility of artemisinin in aqueous media, with a magnitude comparable to that obtained with the best organic solvents. Furthermore, solvatochromic parameters of the ILs aqueous solutions were also measured and combined with COSMO-RS and the cooperative hydrotropy model to establish relations between the artemisinin solubility enhancement and the solvent characteristics. The solubility enhancement of artemisinin is favored by the apolarity of the medium and the lower hydrogen-bond acceptor character of the hydrotrope.

1. Introduction

Malaria is an infectious disease caused, in its most severe form, by the parasite *Plasmodium falciparum* and transmitted to humans by *Anopheles* female mosquitoes. According to the World Health Organization (WHO), about 3.3 billion people are at risk of malaria in their lifetime, particularly in the poorest countries. Although the incidence rate of malaria decreased by 18% between 2010 and 2016 (from 76 to 63 cases per 1000 people at risk), the estimates are that in 2016 malaria reached 216 million people worldwide being responsible for 445 thousand deaths [1].

Artemisinin (Fig. 1) is a compound found in fair amounts in the *Artemisia annua L.* plant, originally from Asia, which has been showing rapid action against the vectors that cause malaria. Its pharmacodynamic and pharmacokinetic characteristics, as well as its strong capacity for *Plasmodium* elimination, have raised many expectations for this new class of antimalarial drugs [2].

Artemisinin extraction is under a great deal of attention from the scientific and technological communities [3–5]. Traditional extraction methods involve the use of hydrocarbons such as hexane or petroleum ether [6], the later considered to be the most suitable due to its wide availability and a good solvation of the target molecule when extracting it from the plant [7]. However, these solvents are highly volatile, flammable, and not friendly for biochemical applications, thus bringing environmental and health concerns [8].

Some alternative extraction methods have emerged, namely low-pressure solid-liquid extractions with ethanol or poly(ethylene glycols) [9], supercritical carbon dioxide [10–12], aqueous solutions of ionic liquids [13], and deep eutectic solvents (DES) combined with mechanochemical extraction [14]. Prawang and coworkers [15], for instance, applied ultrasonic irradiation to intensify artemisinin extraction with poly(ethylene glycol) (PEG) of different molecular weights to replace traditional solvents, and the method developed shows higher extraction efficiency when compared with conventional Soxhlet extraction procedures. Despite these promising results, considering the use of ionic liquids (ILs) as alternative solvents, there is still plenty of room for improve-

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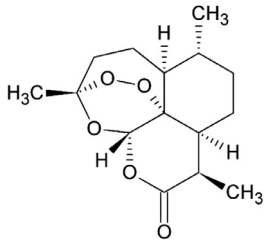

Fig. 1. Molecular structure of artemisinin.

ments as the number of ILs evaluated is very limited. Besides that some technical issues were reported when studying ammonium-based ILs [13], namely residual IL and poor reproducibility when precipitating artemisinin from aqueous solution (much influenced by the high level of extraction of the flavonoid casticin).

Solubility data are among the most useful information when screening solvents for solid-liquid extraction. However, there is little data reported in the literature on the solubility of artemisinin, which is mostly limited to solubility in pure organic solvents [16–18]. Only a few works have explored the solubility of artemisinin in binary aqueous mixed solvents [19,20]. Recently, Laboukhi-Khorsi and co-workers [6] reported the solubility in water, DMSO, propylene glycol, and isopropanol. It was concluded that the highest solubility values at 20°C is in DMSO (103.7 mg·mL^{-1}), while propylene glycol is a very poor solvent (0.6 mg·mL^{-1}) due to its polarity. The solubility data in aqueous solutions are equally important, and Wang et al. [20] reported the solubility data of artemisinin in aqueous ethanol solutions at different temperatures. It was established that solubility increases as the ethanol concentration and the temperature increases.

Water is the most preferable solvent, particularly when dealing with bioactive chemicals. However, the fact that artemisinin is only sparingly soluble in water [6,20] is a major obstacle to its effective use. In this context, hydrotropic compounds can contribute not only to improve the effectiveness of artemisinin extraction, but also to increase its bioavailability, since hydrotropes enhance considerably the solubility levels of hydrophobic solutes in aqueous solutions [21–24].

Recently, ILs have been reported as a promising class of hydrotropes, as both cation and anion contribute to the solubility of hydrophobic compounds in aqueous solution [21,25]. ILs are organic salts with low melting points that may be considered as “designer solvents” since they can be assembled from a multitude of ions [26] to meet the requirements of a specific application. The most frequently studied cations are nitrogen-based, such as pyrrolidinium-, imidazolium-, pyridinium- and quaternary-ammonium-, combined with anions such as chloride (Cl^-), bromide (Br^-), tetrafluoroborate ($[BF_4]^-$), thiocyanate $[SCN]^-$, alkylcarboxylates $[C_nCO_2]^-$, among others. Most extraction works have been focusing on imidazolium-based fluids [27] in the extraction of several compounds such as phenolic acids [28,29], alkaloids [30,31] and triterpenoids [32]. Therefore, it appears that imidazolium-based ILs are promising candidates for increasing the solubility of hydrophobic drugs in aqueous solutions by selecting suitable cation and anion combinations [25].

Amongst the most important features of ILs to be used as solvents in these applications are the solute-solvent interactions usually related to the polarizability and hydrogen-bond ability [33]. Solvatochromic probe studies offer direct information on solvent properties, such as dipolarity/polarizability and hydrogen-bond donating/accepting capabilities [34–36]. The study of physicochemical properties that depend on solute–solvent is much more complex in mixed solvent systems than in pure solvents [37]. The solute can be preferentially solvated by any of the solvents present in the mixture, and solvent–solvent interactions can also strongly affect solute–solvent interactions. This is especially true for hydrotropic systems, where strong water-water interactions lead to solvent-solute aggregation [38]. Therefore, to have a set of parameters characterizing the mixture of two or more compounds, as a pure solvent, is a practical and effective tool to rationalize the solubilization potential of a given solvent towards a family of solutes.

To the best of our knowledge, the use of imidazolium-based ionic liquids as water solubility enhancers for artemisinin was never tested. Due to their success as hydrotropes for phenolic acids and other bioactive compounds [21,25], the current work aims to investigate the anion effect on the solubility of artemisinin in water for ILs containing the 1-butyl-3-methylimidazolium cation. The effect of the ILs concentration and the solvent characteristics described by their solvatochromic parameters were also investigated. Solvatochromic parameters combined with COSMO-RS and the cooperative hydrotropy model were applied to establish relations between the artemisinin solubility enhancement and the solvent characteristics.

2. Experimental section

2.1. Materials

The chemical structures of all ILs studied are depicted in Fig. 2, while the source of the chemicals used, and purity as given by the suppliers, are shown in Table 1. The ILs were dried in a vacuum line (0.1 Pa and 353.15 K) for 48 h prior to their use (the water content of the ILs measured by Karl-Fischer is less than 1500 ppm

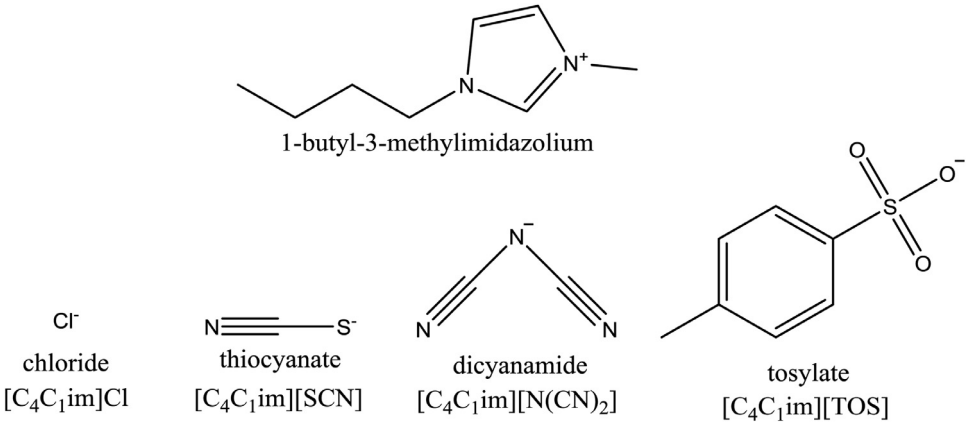

Fig. 2. The cation and the anions of the ILs studied as hydrotropes.

Table 1
Properties of the chemicals used, supplier, CAS and minimum purity.

Compound	Supplier	CAS	Purity (wt%)
1-butyl-3-methylimidazolium thiocyanate - $[C_4C_1im][SCN]$	Iolitec	344790-87-0	99
1-butyl-3-methylimidazolium tosylate - $[C_4C_1im][TOS]$	Iolitec	410522-18-8	99
1-butyl-3-methylimidazolium chloride - $[C_4C_1im]Cl$	Iolitec	79917-90-1	99
1-butyl-3-methylimidazolium dicyanamide - $[C_4C_1im][N(CN)_2]$	Iolitec	448245-52-1	99
Acetonitrile	Fisher Scientific	75-05-8	99
Acetone	VWR Chemicals	67-64-1	99
Ethanol	Fisher Scientific	64-17-5	98
Ethylene glycol	Fluka	107-21-1	99
Poly(ethylene glycol) 400	Acros Organics	25322-68-3	99
Artemisinin	Kang Biothec	63968-64-9	99

in mass). Ultrapure water was used, which was doubly distilled, passed through a reverse osmosis system and treated in Milli-Q plus 185 water purification equipment.

X-ray analyzes at 150 K were initially performed on artemisinin to determine its crystal structure. This compound has orthorhombic structure, space group $P2_12_12_1$, and with cell parameters (a = 6.29 Å; b = 9.25 Å; c = 23.78 Å; $\alpha = \beta = \gamma = 90°$), corresponding to the same structure as described in the literature [39]. The study of the solid phase recrystallized from the saturated solution revealed that artemisinin retained the crystal structure of the original compound, indicating that the solvents studied do not alter the solid phase structure of the compound.

2.2. Solubility of artemisinin

To test and validate the methodology, and to compare the performance of the proposed ILs with conventional solvents, the solubility of artemisinin was initially determined for organic solvents, namely ethylene glycol, polyethylene glycol 400 (PEG400), ethanol and acetone, either in its pure state or in aqueous solutions (50:50 volume%, at 293.2 K).

Aqueous solutions containing the ILs were prepared gravimetrically, using a Mettler Toledo XS205 Dual Range balance (repeatability of 0.015 mg). Artemisinin in small excess to the solubility limit was added to each eppendorf with the solutions and dispersed using a vortex. The system was left with constant stirring (750 rpm) and temperature of (303.2 ± 0.5) K for 72 h in the Eppendorf Thermomixer Comfort equipment, thus ensuring the saturation of artemisinin in the solution. To find the optimal time required for equilibration the mass of artemisinin dissolved was measured, after several time periods, and the adequate time selected accordingly. After, the samples were centrifuged at 4500 rpm and (303.2 ± 0.5) K for 20 min using a Thermo Scientific Heraeus Megafuge 16R centrifuge. For each solvent, three independent saturation solutions were prepared.

The saturated solution was finally sampled, and a filtration step was performed using syringe filters (0.45 c;m) acquired at Whatman, and after diluted in a mixture of acetonitrile and ultrapure water in a volumetric ratio of 40:60 when required. The quantification of artemisinin in each solution was carried out by HPLC-DAD (Shimadzu, model PROMINENCE). HPLC analyses were performed with an analytical C18 reversed-phase column (250 × 4.60 mm), kinetex 5 c;m C18 100 A, from Phenomenex. The mobile phase consisted of 40% of acetonitrile and 60% of ultra-pure water. The separation was conducted in isocratic mode, at a flow rate of 1.0 $mL{\cdot}min^{-1}$ and using an injection volume of 10 c;L. DAD was set at 210 nm [25,40]. Each sample was analyzed at least in duplicate. The column oven and the autosampler were operated at a controlled temperature of 30°C. At these conditions, artemisinin displays a retention time of around 6 min. To check the accuracy of the analytical method, solutions of fixed known concentrations of artemisinin were prepared, and after measured by HPLC. The deviations between the real and measured concentration was always below to 1.7%.

2.3. Solvatochromic parameters

The solvatochromic parameters were measured for the water and IL aqueous solutions. To obtain the parameter α (hydrogen-bond donating ability), the probe pyridine-N-oxide (PyO) was used, and following standard procedures determined by ^{13}C nuclear magnetic resonance (NMR) spectra, using a Bruker Avance 300 equipment operating at 75 MHz, deuterium oxide (D_2O) as solvent and trimethylsilyl propanoic acid (TSP) as the internal reference. The ^{13}C NMR chemical shifts δ(Ci) in ppm of the carbon atoms in positions i = 2 and 4 of pyridine-N-oxide were determined, and α was calculated using Eq. (1) [33,41,42].

$$\alpha = -0.15 \cdot d_{24} + 2.32 \quad (1)$$

where $d_{24} = \delta_4 - \delta_2$.

The parameter β (hydrogen-bond acceptor ability) and π^* (solvent dipolarity/polarizability) were determined using the N,N-diethyl-4-nitroaniline (N,N) and 4-nitroaniline (4N) dyes, respectively. After vigorous stirring for the complete dissolution of the dyes, samples were scanned by UV-V is spectrophotometer (BioTeck Synergy HT microplate reader). The longest wavelength absorption band of each probe was used in Eqs. (2) to (4) to determine the correspondent parameters.

$$\beta = \frac{\left(\Delta\nu_{N,N}^{IL} - \Delta\nu_{N,N}^{cyclohexane}\right) \cdot 0.76}{\Delta\nu_{N,N}^{DMSO} - \Delta\nu_{N,N}^{cyclohexane}} \quad (2)$$

$$\Delta\nu = \Delta\nu_{N,N} - \Delta\nu_{4N} \quad (3)$$

$$\pi^* = \frac{\left(\Delta\nu_{N,N}^{IL} - \Delta\nu_{N,N}^{cyclohexane}\right)}{\Delta\nu_{N,N}^{DMSO} - \Delta\nu_{N,N}^{cyclohexane}} \quad (4)$$

where, ν is the experimental wave number, and the superscripts IL, cyclohexane, and DMSO are correspondent to the values found in these solvents.

3. Results and discussion

3.1. Solubility of artemisinin

Due to its relevance for the present study, the solubility of artemisinin in pure water was firstly determined. The value obtained was (61.83 ± 4.33) $mg.L^{-1}$ at (303.2 ± 0.5) K, which is within the range of values found in the literature [6,43–46], as shown in Fig. S1 in the Supporting Information (SI). It should be however remarked that there is still high uncertainty in the water solubility value of artemisinin with reported values ranging from 13 to 48 $mg.L^{-1}$ at 310.15 K [44–46].

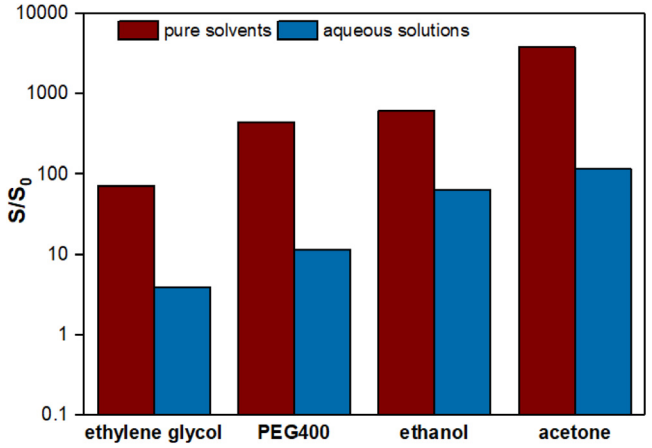

Fig. 3. Relative solubility, expressed as the ratio between solubility of artemisinin in the solvent (S) and the solubility in pure water (S_0) at (303.2 ± 0.5) K: pure solvents and in aqueous solutions (50:50 v/v).

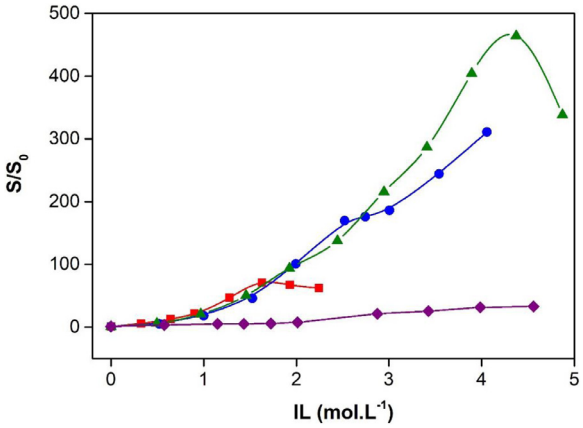

Fig. 4. Influence of the IL molality on the relative solubility, expressed as the ratio between solubility of artemisinin in the solvent (S) and the solubility in pure water (S_0), in aqueous solutions of: ■ [C_4C_1im][TOS]; ● [C_4C_1im][SCN]; ▲ [C_4C_1im][$N(CN)_2$]; ◆ [C_4C_1im]Cl, at (303.2 ± 0.5) K. The lines are only a guide to the eyes.

The results found for the solubility of artemisinin in organic solvents can be seen in Fig. 3 (detailed values provided in Table S1 of SI) expressed as S/S_0, where S and S_0 correspond to the solubility of artemisinin in the solvent (S) and the solubility in pure water (S_0), respectively. Solubility values increase in the following order: ethylene glycol < PEG 400 < ethanol < acetone. Comparing the results found with those reported in the literature, the values obtained are similar to those obtained by Qu et al. [18] and Liu et al. [16]. It is pertinent to highlight again the large discrepancies of the solubility of artemisinin in organic solvents (Fig. S2 and S3 in the SI) found by different researchers. This is most probably related with the purity and source of the artemisinin, but the analytical technique and the difficulty to study highly volatile organic solvents may also play a role.

The high solubility of artemisinin in organic solvents, most notably in acetone, is evident in Fig. 3. However, it is also noticeable the sharp decrease in the solubility in mixtures of the same organic solvents with water at the same temperature (Fig. 3). This highlights the need to find other substances able to increase the solubility of artemisinin in aqueous media which, in this work, has been attempted using imidazolium-based ILs.

In order to evaluate the potential of ILs as hydrotropes, the solubility of artemisinin in the various aqueous ILs solutions was determined. The set of ILs studied here was chosen to assess the impact of the nature of the anion on the artemisinin solubility, which is shown in Fig. 4, while the complete data is compiled in Table S2 in the SI.

From the ILs studied, [C_4C_1im][$N(CN)_2$] and [C_4C_1im][SCN] showed to be very promising hydrotropes for artemisinin, with the artemisinin solubility increase reaching almost 500 times over the water solubility value. Contrarily to the effect of [C_4C_1im]Cl on the solubility of gallic acid or vanillin [21], this IL has the lowest impact on artemisinin solubility among the ILs studied. The ranking observed for the effect of the IL on the solubility of artemisinin ([C_4C_1im][$N(CN)_2$] > [C_4C_1im][SCN] > [C_4C_1im][TOS] > [C_4C_1im]Cl) is similar to that observed for the increase of ibuprofen solubility in water [25].

The aqueous solution of [C_4C_1im][TOS], [C_4C_1im][SCN] and [C_4C_1im][$N(CN)_2$] lead to a significant increase on the solubility of artemisinin at concentrations above 1 mol.L^{-1}. Some authors consider this concentration to be the minimum hydrotropic concentration (MHC), the concentration above which there is a significant increase in the solubility [22,47,48], but in general they fail to relate the MHC to some physical-chemical properties changes of the solvent, making this concept of little use. In this line, some authors have questioned the real existence of an MHC [49–51].

The increase in the solubility of artemisinin in some of the aqueous solutions does not follows a monotonous trend along the IL composition, with the solubility in the [C_4C_1im][TOS] aqueous solutions starting to decrease above 1.5 mol.L^{-1} and in the [C_4C_1im][$N(CN)_2$] above 4 mol.L^{-1}. This effect can probably be explained in terms of self-interactions of the hydrotrope, diminishing its availability to interact with the solute. Another explanation, as recently demonstrated for Cyrene-based systems [52], may

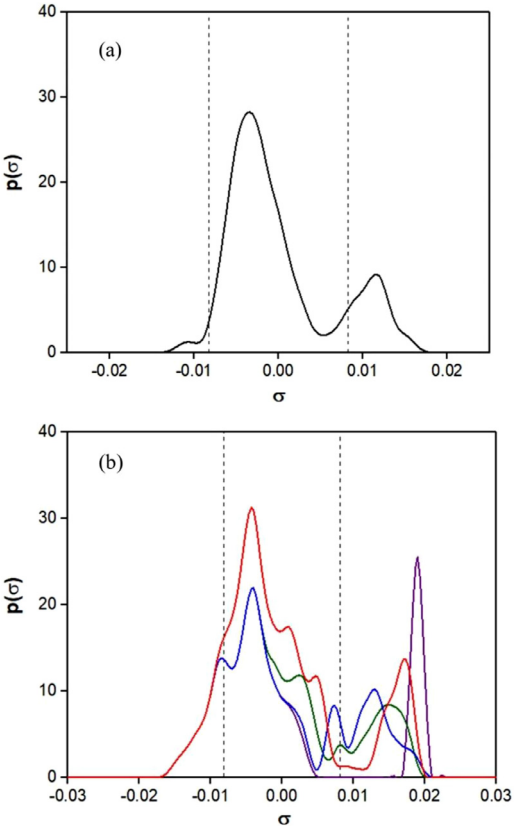

Fig. 5. Sigma Profiles for: (a) Artemisinin (b) [C_4C_1im][TOS] (red); [C_4C_1im][SCN] (blue); [C_4C_1im][$N(CN)_2$] (green); [C_4C_1im]Cl (purple).

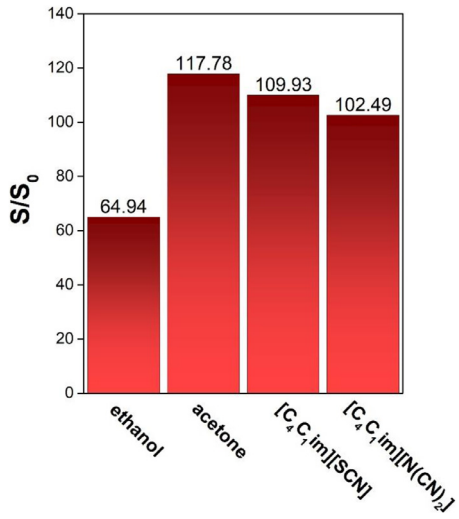

Fig. 6. Relative solubility of artemisinin in aqueous solutions of organic solvents and ILs (around 44 wt%) at (303.2 ± 0.5) K.

be strong three-body interactions between water, solute and hydrotrope, rendering water the cosolvent of the system for high hydrotrope concentration. On the other hand, the solubility in $[C_4C_1im]Cl$ aqueous solutions follow a distinct trend. It is possible to observe that there is only a small continuous increase in the solubility of artemisinin with the IL concentration.

The hydrotropy effect has been explained in terms of the formation of solute-hydrotrope complexes through π–π interactions [53–56], but the water mediation of the interaction between the apolar regions of the hydrotrope with the solute has been gaining evidence [22,38,48]. Aiming at exploring the physical-chemistry of this process, the COSMO-RS sigma profiles (Fig. 5) can provide some support. Concerning artemisinin, it presents a strong peak in the apolar region, almost matching that of $[C_4C_1im][TOS]$, and a shorter peak in the hydrogen-bond acceptor (HBA) region, which is similar to those of $[C_4C_1im][SCN]$ and $[C_4C_1im][N(CN)_2]$. From these profiles it is possible to understand the relevance of the apolar region of the hydrotrope when the IL is diluted in water. The ionic liquid $[C_4C_1im][TOS]$, the most apolar, presents a more pronounced effect, but when the IL concentration increases the dominant aspect favoring the solubilization of artemisinin seems to be the lower HBA character of the hydrotrope. As it is going to be discussed in more detail below, the artemisinin solubility change seems to be also influenced by the polarizability of the solvent.

Fig. 6 shows the solubility enhancement for the 2 best organic solvents and the 2 best ILs studied in this work, at the same weight fraction in water (around 44 wt%). The solubility of artemisinin in aqueous solutions of ILs is comparable to the values of aqueous solutions of acetone (the best organic solvent studied), thus representing an alternative potential solvent to be applied in the artemisinin extraction from biomass while allowing to replace organic volatile solvents.

Recently, the formation of co-aggregates between IL ions and the solute has been proposed as a major contributor to the hydrotropic solubilization [21,25,38], being the Kirkwood-Buff (KB) theory a good foundation to understand the major driving forces behind hydrotropic solubilization [57]. Shimizu and collaborators [22] have suggested a new approach that allows an analogy between hydrotropy and cooperative phenomena which correctly describes the common sigmoidal solubility curves found in hy-

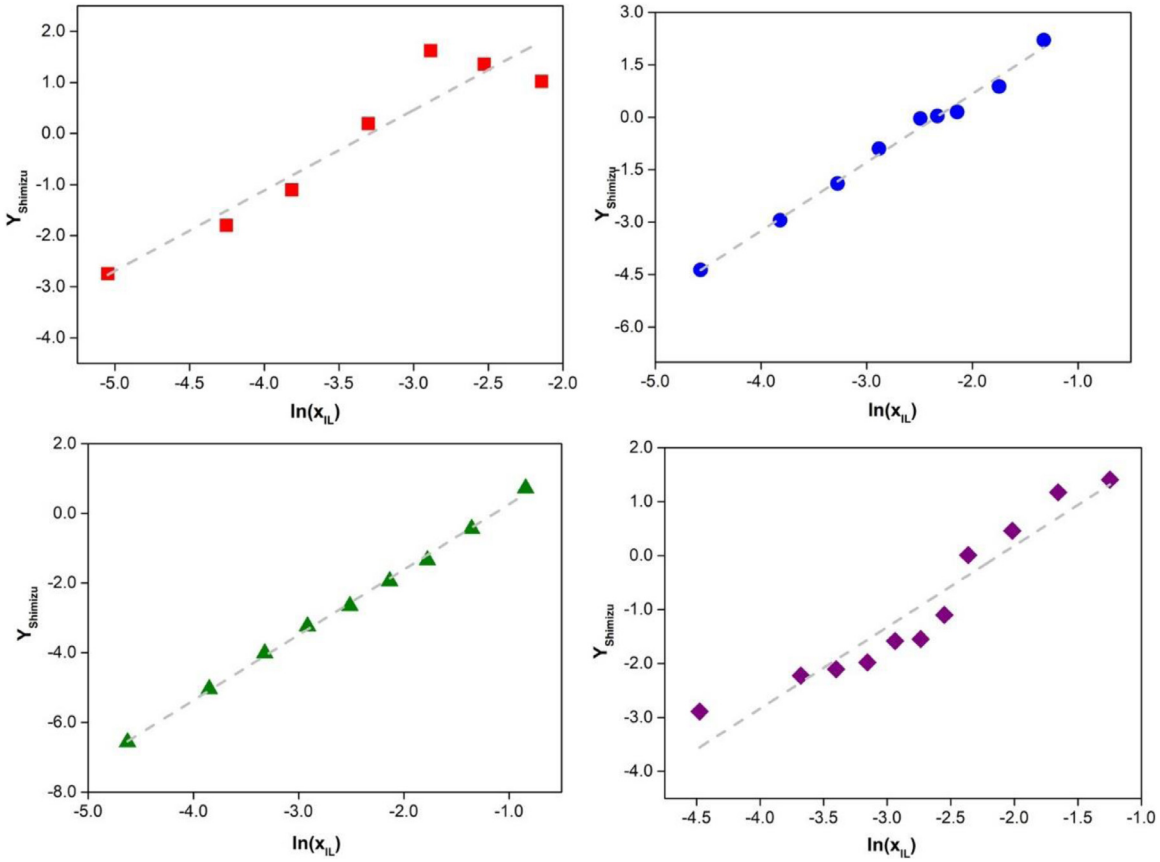

Fig. 7. Linearized plot (Eq. (6)) of the cooperative hydrotropy Shimizu model for: ■ $[C_4C_1im][TOS]$; ● $[C_4C_1im][SCN]$; ▲ $[C_4C_1im][N(CN)_2]$; ◆ $[C_4C_1im]Cl$. The lines are least squares fit with parameters listed in Table S3.

Table 2
Solvatochromic parameters of pure water at 298.2 K and 0.1MPa.[a]

	A	$\beta \pm \sigma$	$\pi^* \pm \sigma$
water	1.37 ± 0.02 (1.17 [58,59];1.23 [60];1.30 [61]; 1.36 [41]; 0.95 [62])	0.16 ± 0.01 (0.47 [58];0.49 [60];0.46 [61]; 0.15 [59,62]; 0.16 [63])	1.27 ± 0.01 (1.09 [58,59];1.14 [60];1.10 [61]; 1.26[41]; 1.31 [62])

[a] Temperature and pressure standard uncertainties are $u(T) = 0.1$ K and $u_r(p) = 0.05$.

drotropy, and is established through the linearization presented in equation 6:

$$Y_{Shimizu} = \ln\left[\frac{1-\frac{S}{S_0}}{\frac{S}{S_0}-\left(\frac{S}{S_0}\right)_{max}}\right] = m \cdot \ln x_{IL} + b \quad (6)$$

where x_{IL} represents the mole fraction of the hydrotrope in the aqueous solution, and S and S_0 represent the solubility of artemisinin in the hydrotrope solution and water, respectively.

The procedure used to estimate the parameters of the model has been given in detail in previous works. As shown in Fig. 7, generally the linearization presents satisfactory results, being of much better quality in the ILs where the apolar interactions are more significant, presenting less hydrogen-bonding acceptor character. In fact, for the two ILs presenting higher solubility enhancement ($[C_4C_1im][N(CN)_2]$ and $[C_4C_1im][SCN]$) the fit is of very good quality, thus suggesting the validity of the assumptions made by Shimizu et al. [22] for cooperative phenomena (Table S3 in the SI compiles the estimated parameters). The representation of the relative solubility of artemisinin over the whole range of hydrotropic concentrations studied is shown in Fig. S4 in the SI, confirming the good fitting.

3.2. Solvatochromic parameters

In order to improve the understanding of the solubility enhancement of artemisinin and the solvent-solute interactions behind it, the Kamlet-Taft empirical parameters, α (hydrogen-bond donor, HBD), β (HBA), and dipolarity/polarizability (π^*), were also determined. The parameters were firstly measured for pure water and are reported and compared to literature values in Table 2.

Table 2 shows that it is quite common to find different values of the Kamlet–Taft parameters for the same solvent. It has been shown that differences can be easily related to the different dyes used [64]. In fact, Lu et al. [59] used 4-nitroanisole to determine the π^* parameter, a dichloro-substituted betaine dye to find α and 4-nitroaniline and N,N-dimethyl-4-nitroaniline to obtain the β. The choice of the probe led to a difference between the data found for the HBD and dipolarity/polarizability parameters; however, the HBA parameter shows conformity in the results, possibly because the same dye has been used in both works. Despite these differences, it should be remarked that the Kamlet–Taft parameters, when determined under the same conditions, provide a qualitative trend of a given set of solvents. The α, β, and π^* values were determined for different ILs aqueous solutions, being the IL concentration effect represented in Fig. 8 (numerical values are compiled in Table S4 in the SI).

From the results obtained it can be seen that the tosylate anion confers the highest hydrogen donor and acceptor character to the IL aqueous solutions, while $[N(CN)_2]^-$ and $[SCN]^-$ show the opposite effect. Furthermore, the α values generally decrease with increasing the concentration of IL in aqueous solution, which is in agreement with the calculated COSMO-RS sigma profiles (ILs are

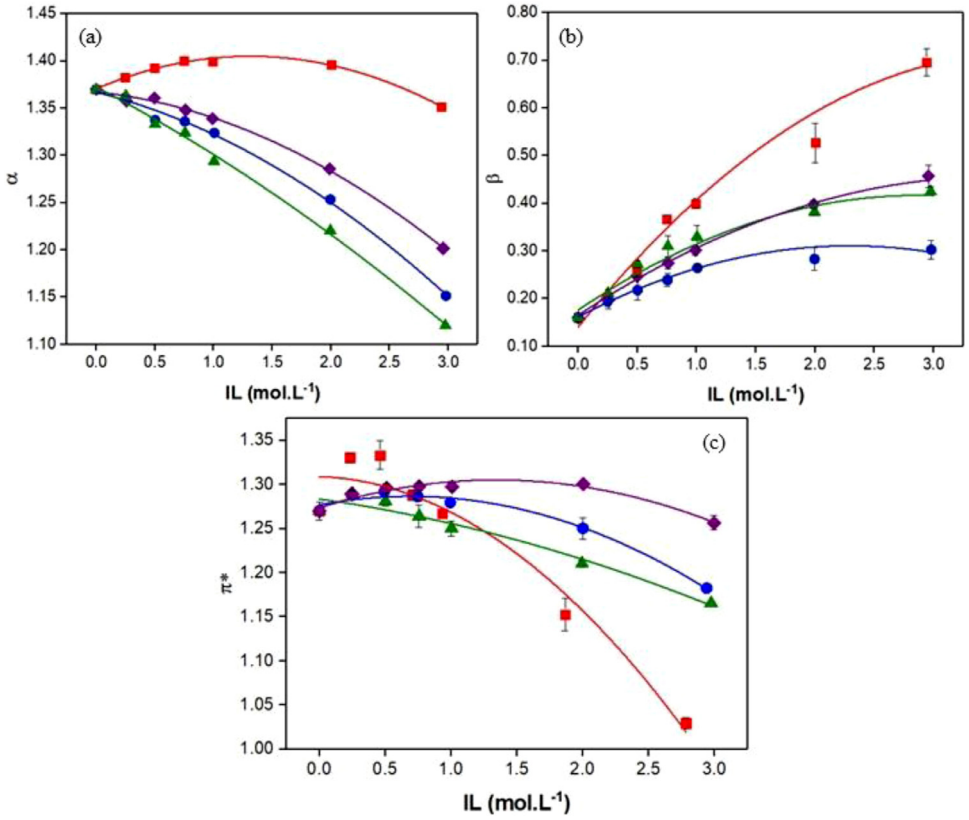

Fig. 8. Solvatochromic parameters at 298.2 K, namely (a) α; (b) β and (c) π^*, for aqueous solutions of: ■ $[C_4C_1im][TOS]$; ● $[C_4C_1im][SCN]$; ▲ $[C_4C_1im][N(CN)_2]$; ◆ $[C_4C_1im]Cl$.

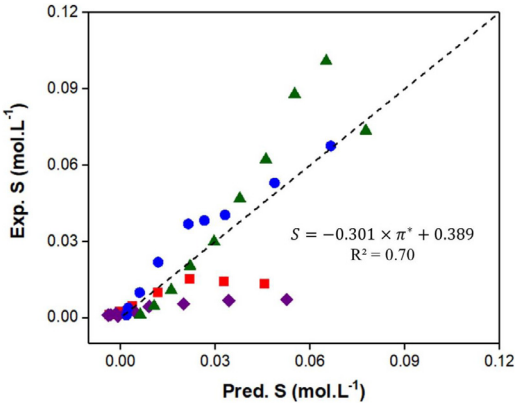

Fig. 9. Correlation between experimental and predicted solubility data of artemisinin in aqueous solutions of: ■ $[C_4C_1im][TOS]$; ● $[C_4C_1im][SCN]$; ▲ $[C_4C_1im][N(CN)_2]$; ◆ $[C_4C_1im]Cl$.

better HBA thus contributing to decrease the HBD character of water). It has been reported [42,64] that the main effect on α is attributed to the cation, but it is here shown that the IL anion effect also plays a relevant role in aqueous solution. Concerning the dipolarity/polarizability parameter, the IL containing $[TOS]^-$ is the one presenting a more pronounced change with IL molality, and that containing Cl^- the less, which is most probably related to the more pronounced and large apolar region in $[TOS]^-$, while the $[C_4C_1im]Cl$ IL presents the smaller, as shown by the COSMO-RS sigma profiles.

Trying to establish a relation between the artemisinin solubility change and the solvatochromic parameters, a multiple linear correlation methodology has been implemented. It was first attempted the correlation of the solubility in all four solvents with each parameter individually. The correlations with α and β show no improvement over a simple correlation with the IL concentration. However, when using the π^* parameter only, a very good correlation is obtained, which improves only slightly if combined with α or β. Fig. 9 shows the experimental solubility data *versus* the predicted solubility data for the best correlation using the π^* parameter only, while in Fig. S5 of the SI it is possible to compare with the much worse correlations using only α or β, and the slightly improvement when combining one of those with π^*. A better fitting occurs for ILs leading to a higher artemisinin solubility. These results confirm the interpretation given before for the hydrotropic phenomena, as the π^* parameter is intimately related to the medium apolarity conferred by the hydrotrope (IL).

4. Conclusions

The present work focuses on the study of imidazolium-based ILs as potential hydrotropes for artemisinin. The results obtained show the excellent ability of $[C_4C_1im][SCN]$ and $[C_4C_1im][N(CN)_2]$ ILs to act as hydrotropes, increasing the solubility of artemisinin in aqueous solution up to 460-fold, being comparable to the best organic solvents identified so far in aqueous solutions.

The IL molality effect on the artemisinin solubility was well described by the Kirkwood–Buff based cooperative hydrotropy model, more evidently for the IL leading to higher solubilities. Additionally, the combination of COSMO-RS analysis and the determination of solvatochromic parameters allowed to identify that the apolarity of the medium is an essential aspect affecting the increase of artemisinin solubility, while the dominant factor favoring the solubilization of artemisinin at higher hydrotrope concentration is its lower hydrogen-bond acceptor character.

The considerable increase of artemisinin solubility in water using $[C_4C_1im][SCN]$ or $[C_4C_1im][N(CN)_2]$ suggests that aqueous solutions of ILs may be promising solvents for the sustainable extraction of artemisinin from *Artemisia annua L.*

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Isabela Sales: Investigation, Writing - original draft, Visualization. **Dinis O. Abranches:** Investigation, Software, Writing - review & editing, Visualization. **Pedro Costa:** Investigation, Writing - review & editing. **Tânia E. Sintra:** Investigation. **Sónia P.M. Ventura:** Investigation, Resources. **Silvana Mattedi:** Investigation, Resources. **João A.P. Coutinho:** Conceptualization, Writing - review & editing, Funding acquisition. **Mara G. Freire:** Conceptualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Simão P. Pinho:** Conceptualization, Writing - original draft, Supervision, Project administration.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.fluid.2021.112961.

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