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Enhanced dissolution of ibuprofen using ionic liquids as catanionic hydrotropes†

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The therapeutic effectiveness of a drug largely depends on its bioavailability, and thus ultimately on its aqueous solubility. Hydrotropes are compounds able to enhance the solubility of hydrophobic substances in aqueous media and therefore are extensively used in the formulation of drugs and personal care products. Recently, some ionic liquids were shown to display a strong ability to enhance the solubility of biomolecules through hydrotropy. In this work, the impact of the ionic liquid chemical structures and their concentration on the solubility of ibuprofen was evaluated and compared with the performance of conventional hydrotropes. The results obtained clearly evidence the exceptional capacity of ionic liquids to enhance the solubility of ibuprofen. $[C_4C_1im][SCN]$ and $[C_4C_1im][N(CN)_2]$ seem to be the most promising ionic liquids for ibuprofen solubilisation, where an increase in the solubility of 60- and 120-fold was observed with ionic liquid concentrations of *circa* 1 mol kg^{-1}, respectively. Dynamic light scattering and molecular dynamics simulations were used to investigate the mechanism of the IL-mediated drug solubility and the results obtained indicate that the structure of aqueous solutions of ionic liquids and the role it plays in the formation of ionic liquid-drug aggregates is the mechanism driving the hydrotropic dissolution.

Introduction

The solubilisation of poorly water-soluble drugs has been a very important issue in the screening of new drugs as well as in their formulation. More than 40% of the failures in the development of new drugs have been attributed to poor biopharmaceutical properties, including poor water solubility.[1] In fact, the therapeutic effectiveness of a drug can be severely limited by its aqueous solubility.[2] Among the various approaches employed to enhance the aqueous solubility of poorly water-soluble drugs, such as the use of surfactants, salt forms and change of pH, the hydrotropic solubilisation is one of the most studied due to its simplicity and efficiency.[3] Furthermore, hydrotropes, in general, present low toxicity and low bioaccumulation potential due to their low octanol–water partition coefficients.[4] The term hydrotropic agent was first introduced by Neuberg in 1916.[5] By definition, hydrotropes are compounds capable of substantially increasing the solubility of hydrophobic substances in water. Conventional hydrotropes are typically composed of a hydrophobic aromatic ring with an anionic group (hydrophilic part) where ammonium, calcium, potassium or sodium act as counter ions.[6] The cationic hydrotropes are a minority, an example being the salts of aromatic amines (procaine hydrochloride).[7] Although these compounds exhibit an amphiphilic nature, they are not surfactants. Actually, due to their short hydrophobic moiety, hydrotropes have a weak tendency to self-aggregate in water and therefore do not form micelles, nor do they present a CMC.[8] Despite the large number of reviews addressing hydrotropy, its mechanism of action is not yet clearly understood.[3,9,10] Three main hypotheses have been proposed in order to explain the hydrotropic-mediated solubilisation. Some authors justify this phenomenon with the formation of a complex between the solute and the hydrotrope.[11,12] On the other hand, some works suggest that the hydrotropes may change the solvent structure around the solute and can be therefore considered as structure makers or breakers.[13,14] In recent years, co-aggregation of the solute with the hydrotropes above a minimum hydrotrope concentration (MHC) has been proposed as the main mechanism behind the enhanced solubility.[15–21] The MHC of a hydrotrope is considered as a measure of the stability of its aggregation form relative to its monomeric form. Thus, the lower the MHC, the greater the hydrotrope stability.[3]

During the last few years, the application of ionic liquids (ILs) has extended from solvents in "green" chemistry to pharmaceutical applications with the ultimate aim to improve

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the active pharmaceutical ingredient (API) dissolution, solubility and bioavailability and to prevent polymorphism.[22–30] Rengstl and co-authors showed the capacity of the short chain choline carboxylates to act as hydrotropes for Disperse Red 13, a hydrophobic dye.[31] Recently, ILs were reported as a promising class of catanionic hydrotropes since both the IL cation and anion contribute to enhance the solubility of hydrophobic compounds in aqueous solution.[32] The aqueous solutions of ILs showed a much higher capacity to solubilize the two antioxidants studied than any of the pure solvents, with solubility enhancements of up to 40-fold.[32] In this context, ILs appear as promising candidates to enhance the aqueous solubility of hydrophobic drugs by the selection of the adequate cation/anion combinations.

The present work proposes to investigate the effect of the IL chemical structures and their concentration on the solubility of ibuprofen, a poorly water-soluble compound whose chemical structure is shown in Fig. 1. This anti-inflammatory drug belongs to BCS Class II (BCS 2), which are characterized by low solubility and high permeability.[33] To achieve acceptable absorption after oral administration, APIs should present both, enough aqueous solubility and permeability through gastrointestinal mucosa.[34] Therefore, solubility improvement is a powerful formulation strategy for compounds of this class to optimize their biopharmaceutical profiles.[34,35] Finally, the hydrotropic solubilization mechanism induced by ILs for ibuprofen is investigated using molecular dynamics simulations.

Experimental section

Materials

In this work, ten ILs were investigated in terms of their capacity to enhance the solubility of ibuprofen in water, namely 1-butyl-3-methylimidazolium thiocyanate, [C_4C_1im][SCN]; 1-butyl-3-methylimidazolium tosylate, [C_4C_1im][TOS]; 1-butyl-3-methylimidazolium chloride, [C_4C_1im]Cl; 1-butyl-3-methylimidazolium dicyanamide, [C_4C_1im][$N(CN)_2$]; 1-butyl-3-methylpyridinium chloride, [C_4C_1py]Cl; 1-butyl-1-methylpiperidinium chloride, [C_4C_1pip]Cl; 1-butyl-1-methylpyrrolidinium chloride, [C_4C_1pyrr]Cl; tetrabutylammonium chloride, [$N_{4,4,4,4}$]Cl; tetrabutylphosphonium chloride, [$P_{4,4,4,4}$]Cl; and cholinium chloride, [$N_{1,1,1,2(OH)}$]Cl. The imidazolium-, pyridinium-, piperidinium- and pyrrolidinium-based ILs were purchased from Iolitec. [$N_{4,4,4,4}$]Cl and [$N_{1,1,1,2(OH)}$]Cl were obtained from Sigma-Aldrich. [$P_{4,4,4,4}$]Cl was kindly supplied by Cytec Industries Inc. The ILs used have a stated supplier purity of at least 98 wt%, which was further checked by their ^{1}H and ^{13}C NMR spectra. Sodium thiocyanate, Na[SCN] (98.0 wt% pure), was supplied by Fluka; sodium tosylate, Na[TOS] (95.0 wt% pure), was from TCI; and sodium dicyanamide, Na[$N(CN)_2$] (96.0 wt% pure), was from Sigma-Aldrich. Ibuprofen (98.0 wt% pure) was supplied by Sigma-Aldrich. The mobile phase used in the HPLC analysis was composed of ammonium acetate (99.99 wt% pure) and acetic acid (99.99 wt% pure), both from Sigma-Aldrich, HPLC grade acetonitrile from HiPerSolv Chromanorm® and

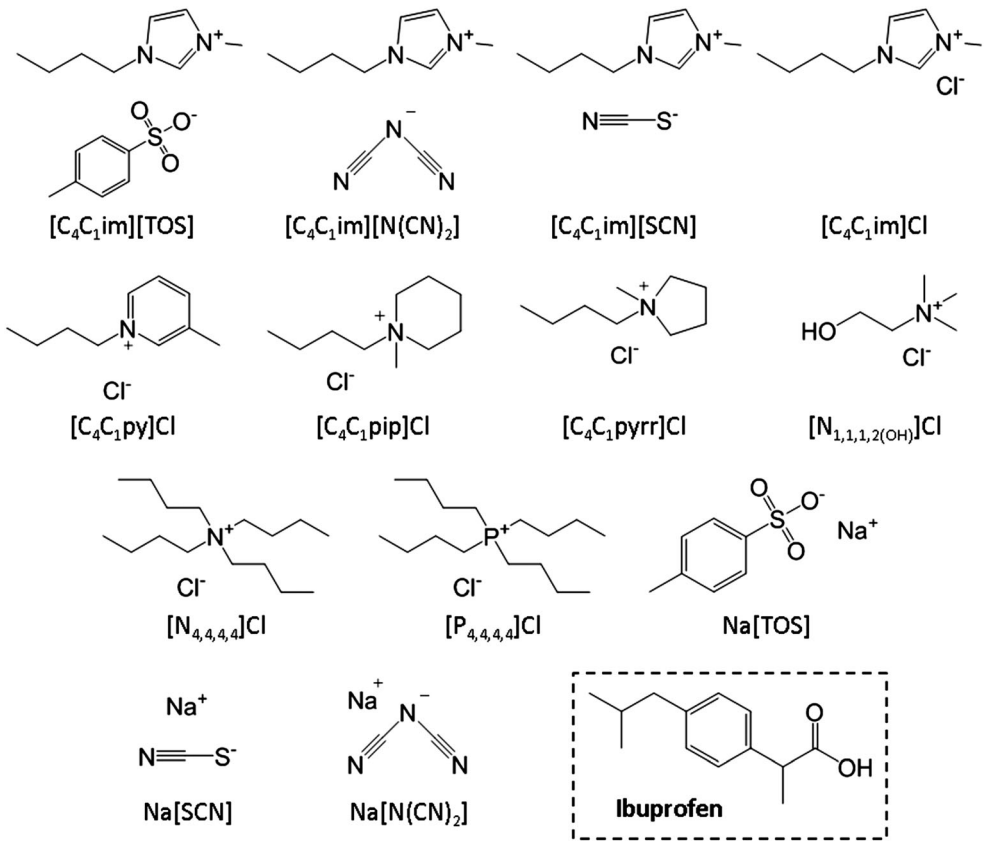

Fig. 1 Chemical structure of the ILs and salts studied as hydrotropes and ibuprofen.

ultrapure water, which was double distilled, passed by a reverse osmosis system and further treated with a Milli-Q plus 185 water purification apparatus. The ionic structures of all ILs and salts studied are depicted in Fig. 1. The filters used during the filtration steps were syringe filters (0.45 μm) and regenerated cellulose membrane filters (0.45 μm), acquired at Specanalitica and Sartorius Stedim Biotech, respectively.

Solubility of ibuprofen

Ibuprofen was added in excess to the IL aqueous solutions or pure water. Then, it was equilibrated in an air oven at (303.1 ± 0.5) K, under constant agitation (750 rpm) and an equilibration time of 72 h, using Eppendorf Thermomixer Comfort equipment. The equilibration conditions were previously optimized. After saturation was achieved, all samples were centrifuged at (303.1 ± 0.5) K for 20 minutes at 4500 rpm, using a Hettich Mikro 120 centrifuge. In order to quantify the pharmaceutical drug, the samples of the liquid phase were collected and filtered using syringe filters, to remove all solid particles in suspension. The saturated solution was diluted in a mixture of acetonitrile and ultrapure water in a volumetric ratio of 30 : 70 when required, and the amount of ibuprofen was quantified by HPLC-DAD (HPLC Elite LaChrom, VWR Hitachi, with a diode array detector l-2455), using an analytical method previously developed by our group.[36] DAD was set to measure the amount of ibuprofen at 230 nm using a calibration curve previously established, and the results are reported in the ESI,† Table S1. Each assay was performed in triplicate.

Dynamic light scattering (DLS)

To evaluate the presence of IL–solute aggregates, as well as to determine their size, aqueous solutions with 2.5 mol kg^{-1} of $[C_4C_1im][N(CN)_2]$/$[C_4C_1im][SCN]$ were prepared and saturated with ibuprofen at 303 K. The saturated solutions were filtrated using a 0.45 μm PTFE membrane and then analyzed by dynamic light scattering (DLS) using a Malvern Zetasizer Nano-ZS from Malvern Instruments. Samples were irradiated with red light (HeNe laser, wavelength of 565 nm) and the intensity fluctuations of the scattering light (detected at a backscattering angle of 173°) were analyzed to obtain an autocorrelation function. The respective software (DTS v 7.03) provides the particles' average size and their distribution. The radii of each aggregate were determined from the DLS measurements using the Stokes–Einstein equation assuming spherical aggregates, and a low volume fraction of the dispersed phase. Consequently, the determined values must be considered with caution and regarded as approximate ones. Samples were measured in disposable polystyrene cuvettes at a temperature of 303 K. Data were then acquired in the automatic mode, ensuring that enough photons were accumulated for the result to be statistically relevant. The software also incorporates a 'data quality report'. The solution viscosities and refractive indexes were previously measured by the DLS measurements.

Crystal structure analysis

A suitable amount of ibuprofen was dissolved in 2 mL of the solvent ($[C_4C_1im][SCN]$ with 2.5 mol kg^{-1} or ethanol). In order to precipitate the drug, an equal volume of cold water was added. The crystals were analyzed in solution and after their filtration using a BX51 Olympus optical microscope (Olympus Co., Tokyo, Japan). The crystals were further investigated through (i) powder X-ray diffractometry using an Empyrean powder diffractometer (PANalytical, Almelo, Netherlands) at room temperature, with nickel filter, Cu-Kα radiation (λ = 1.54180 Å), step-scanned in 0.04° (2θ) at each 30 s; and (ii) single crystal X-ray diffraction at 180 K with monochromated Mo-K_α radiation (λ = 0.71073 Å) on a Bruker SMART Apex II diffractometer (Bruker, Billerica, USA) equipped with a CCD area detector.

Molecular dynamics (MD) simulations

The atomistic description of water, ibuprofen and the $[C_4C_1im][N(CN)_2]$ and $[C_4C_1im][SCN]$ ionic liquids was implemented using the SPC,[37] OPLS[38] and CL&P[39–41] force-fields, respectively. The MD simulations were carried out using the DL_POLY 2.20[42] and Gromacs[43–45] packages.

The runs in DL_POLY (systems 1 to 5 in Table 1) started from low-density configurations and were performed using 2 fs time-steps and 2 nm cutoff distances, with Ewald summation corrections performed beyond the cutoffs. All simulations were subjected to equilibration runs under isobaric isothermal ensemble conditions (p = 0.1 MPa and T = 300 K with Nosé–Hoover thermostats and barostats with relaxation time constants of 1 and 4 ps, respectively). After 1.3 ns, the density of each system reached constant and consistent values, indicating that equilibrium had been attained and possible ergodicity problems had been overcome. Finally, at least six consecutive production stages of 1.0 ns each were performed, and the combined results were used for the aggregation analyses of all studied ionic liquids (see below).

Gromacs simulations (systems 6 to 8 in Table 1) were started from configurations built with the PACKMOL package[46] and were performed using 1 fs time-steps and 2 nm cutoff distances,

Table 1 Simulation conditions, size of the equilibrated boxes and concentrations

	System	n_{Ibu}	n_{IL}	n_w	l_{box} nm	V_{box} nm^3	[Ibu] mol L^{-1}	[IL] mol L^{-1}
1	$[C_4C_1im][N(CN)_2]$ + water	0	101	4600	5.568	172.6	0.000	0.971
2	$[C_4C_1im][SCN]$ + water	0	105	4600	5.566	172.4	0.000	1.011
3	Ibuprofen + water	130	0	4600	5.696	184.8	1.168	0.000
4	$[N(CN)_2]$-based ternary	130	101	4600	6.000	216.0	0.999	0.776
5	[SCN]-based ternary	130	105	4600	5.988	214.7	1.005	0.812
6	Ibuprofen + water	10	0	4600	5.246	144.3	0.115	0.000
7	$[N(CN)_2]$-based ternary	10	101	4600	5.631	178.5	0.093	0.939
8	[SCN]-based ternary	10	105	4600	5.597	175.3	0.095	0.994

with Ewald summation corrections performed beyond the cut-offs. The isothermal–isobaric ensemble conditions used during equilibration were p = 0.1 MPa and T = 300 K with Nosé–Hoover thermostats and Parrinello–Rahman barostats with relaxation time constants of 1 and 4 ps, respectively. The systems were equilibrated for 4 ns and six consecutive production runs of 1.0 ns each were carried out.

The aggregation analyses of the $[C_4C_1im][N(CN)_2]$ and $[C_4C_1im][SCN]$ ionic liquids and their mixtures with water and ibuprofen focused on four types of issues: (i) the evaluation of the connectivity between the charged moieties of the molecular ions that compose the so-called polar network; (ii) the evaluation of the connectivity within the molecular solute and an estimation of the corresponding aggregate size; (iii) the calculation of the connectivity between the molecular solute and the ionic liquids; and (iv) the evaluation of the connectivity between the anion of the ionic liquids and water. The connectivity analyses are based on algorithms[32,47,48] previously described based on neighbour lists and interaction distance criteria, adapted to take into account the interaction centres of ibuprofen.

Results and discussion

In order to evaluate the hydrotropic capability of ILs for the dissolution of hydrophobic drugs, the solubility of ibuprofen was determined in several aqueous solutions of ILs, at various concentrations, and compared with the results obtained with conventional hydrotropes. The value obtained for the solubility of ibuprofen in water at (303.15 ± 0.50) K was (37.54 ± 0.93) mg L^{-1}, which is in good agreement with the literature,[60,61] ranging from 15.48 to 66.84 mg L^{-1} at the same temperature. All the solubility data, as well as the respective standard deviations, are presented in ESI† (Table S2).

Minimum hydrotrope concentration (MHC) is the lowest concentration of hydrotrope required for the solubility of a certain compound in water to start increasing significantly, being used in the interpretation of the hydrotropic behavior.[3] In order to investigate the MHC for $[C_4C_1im][N(CN)_2]$, $[C_4C_1im]$-$[SCN]$, $[P_{4,4,4,4}]Cl$, $[C_4C_1pip]Cl$ and $[C_4C_1pyrr]Cl$, the solubility of ibuprofen was measured in aqueous solution with hydrotrope concentrations between 0.02 and 1.3 $mol_{Hyd}\ kg_{water}^{-1}$. According to the slope changes observed in Fig. 2, the MHC value appears to be approximately 0.10 mol kg_{water}^{-1} for $[C_4C_1im][N(CN)_2]$ and $[C_4C_1im][SCN]$, and 0.18 mol kg_{water}^{-1} for $[P_{4,4,4,4}]Cl$. On the other hand, a continuous variation in the solubility of ibuprofen was observed for $[C_4C_1pip]Cl$ and $[C_4C_1pyrr]Cl$. In fact, although the MHC has been extensively used, various authors have been recently questioning this concept and relate it with less accurate experimental measurements (such as due to the presence of impurities) and with an incorrect interpretation of the experimental data.[21,32,49–52]

The set of ILs here investigated were chosen to evaluate the influence of the anion nature and the cation core upon their capacity to enhance the solubility of the drug. The results of the influence of ILs, as well as some common hydrotropes, on the solubility enhancement of ibuprofen are presented in Fig. 3. It is shown that their performance as hydrotropes is much superior to that of conventional hydrotropes and chaotropic (salting-in inducing) salts (Na[TOS], Na[SCN], $Na[N(CN)_2]$). In order to obtain a quantitative assessment of the influence of the ILs' chemical structure on the solubility enhancement, the solubility data were correlated with the hydrotrope concentration using the modified Setschenow equation:

$$S/S_0 = 1 + K_{Hyd}C_{Hyd} \quad (1)$$

where S and S_0 are the solubility (mol L^{-1}) of the drug in the hydrotrope aqueous solution and in pure water, respectively, and C_{Hyd} is the concentration of the hydrotrope in aqueous solution ($mol_{Hyd}\ kg_{water}^{-1}$). The hydrotropy constants, K_{Hyd}, and the respective standard deviations, were estimated for each hydrotrope and are listed in Table 2.

This constant can be considered as a measure of the effectiveness of a hydrotrope, in other words, the higher the constant,

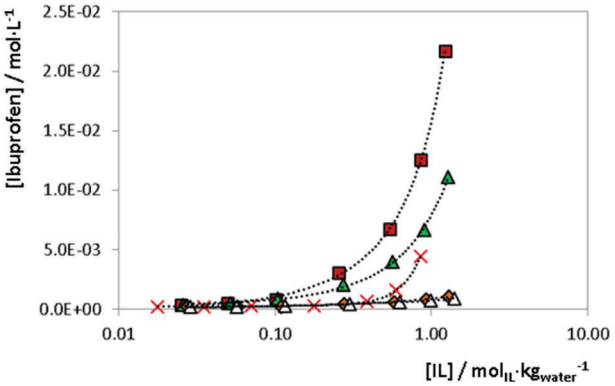

Fig. 2 Impact of the IL concentration on the solubility of ibuprofen in aqueous solutions of (■) $[C_4C_1im][N(CN)_2]$, (▲) $[C_4C_1im][SCN]$, (✕) $[P_{4,4,4,4}]Cl$, (◆) $[C_4C_1pip]Cl$ and (Δ) $[C_4C_1pyrr]Cl$, in order to evaluate the MHC. Lines are guides for the eye.

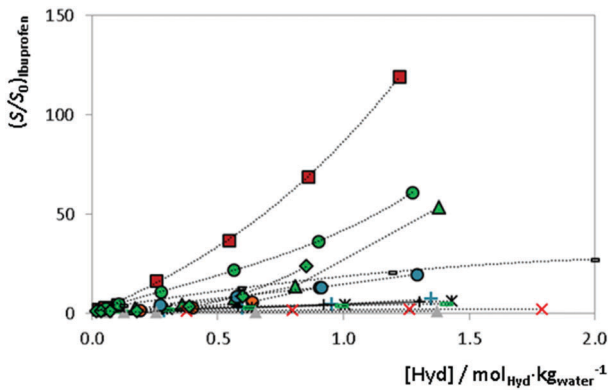

Fig. 3 Impact of the hydrotrope concentration on the solubility of ibuprofen in aqueous solutions of (■) $[C_4C_1im][N(CN)_2]$, (●) $[C_4C_1im][SCN]$, (◆) $[P_{4,4,4,4}]Cl$, (▲) $[C_4C_1im][TOS]$, (■) $Na[N(CN)_2]$, (●) Na[TOS], (●) $[N_{4,4,4,4}]Cl$, (+) $[C_4C_1py]Cl$, (+) $[C_4C_1pip]Cl$, (✳) $[C_4C_1mim]Cl$, (▬) $[C_4C_1pyrr]Cl$, (✕) $[N_{1,1,1,2(OH)}]Cl$ and (▲) Na[SCN]. S and S_0 represent the solubility of the drug in the aqueous solution of the hydrotrope and in water, respectively. Lines are guides for the eye.

Table 2 K_{Hyd} values for the several hydrotropes analysed in the solubility of ibuprofen at (303.1 ± 0.5) K

Hydrotrope	K_{Hyd} (kg_{water} mol_{Hyd}^{-1}) ± σ
$[C_4C_1im][N(CN)_2]$	87.2 ± 5.0
$[C_4C_1im][SCN]$	43.4 ± 1.7
$[C_4C_1im][TOS]$	28.9 ± 5.8
$[C_4C_1im]Cl$	3.6 ± 0.1
$[C_4C_1py]Cl$	4.2 ± 0.4
$[C_4C_1pip]Cl$	3.8 ± 0.1
$[C_4C_1pyrr]Cl$	3.0 ± 0.1
$[P_{4,4,4,4}]Cl$	20.0 ± 3.5
$[N_{4,4,4,4}]Cl$	10.7 ± 1.9
$[N_{1,1,1,2(OH)}]Cl$	(7.1 ± 0.7) × 10^{-1}
$Na[N(CN)_2]$	14.6 ± 1.2
Na[TOS]	14.0 ± 0.3
Na[SCN]	(−8.5 ± 2.6) × 10^{-2}

the higher the capacity of the hydrotrope to increase the solubility of a given compound in water. The ability of the various ILs and salts to act as hydrotropes for ibuprofen increases in the following order: $Na[SCN] < [N_{1,1,1,2(OH)}]Cl < [C_4C_1pyrr]Cl < [C_4C_1im]Cl < [C_4C_1pip]Cl < [C_4C_1py]Cl < [N_{4,4,4,4}]Cl < Na[TOS] < Na[N(CN)_2] < [P_{4,4,4,4}]Cl < [C_4C_1im][TOS] < [C_4C_1im][SCN] < [C_4C_1im][N(CN)_2]$.

In order to evaluate the effect of the IL cation on the solubility of ibuprofen, a series of chloride-based ILs were studied and are presented in Fig. 4. The set of IL cations analysed include aromatic ($[C_4C_1im]^+$ and $[C_4C_1py]^+$), cyclic non-aromatic ($[C_4C_1pyrr]^+$ and $[C_4C_1pip]^+$) and non-cyclic non-aromatic ($[N_{4,4,4,4}]^+$, $[P_{4,4,4,4}]^+$ and $[N_{1,1,1,2(OH)}]^+$) compounds. Among the cations investigated in the chloride-based IL series, $[N_{4,4,4,4}]Cl$ and $[P_{4,4,4,4}]Cl$ presented a higher increase in the solubility of the drug studied in this work. The remaining IL cations showed a significant hydrotropic activity for ibuprofen, with the exception of $[N_{1,1,1,2(OH)}]Cl$. The π–π interactions have been used in the past to explain the formation of solute-hydrotrope complexes, and thus the hydrotropic effect.[11,12,53] However, the results obtained here do not support the idea that the π–π interactions between the aromatic drug and the aromatic cation core are the dominant driving forces behind the hydrotropic behavior, since the best results were achieved for non-cyclic non-aromatic ILs, in agreement with previous works.[14,32,54,55] The influence of the IL cation on the hydrotropic constant was further evaluated using the tosylate, thiocyanate and dicyanamide anions,

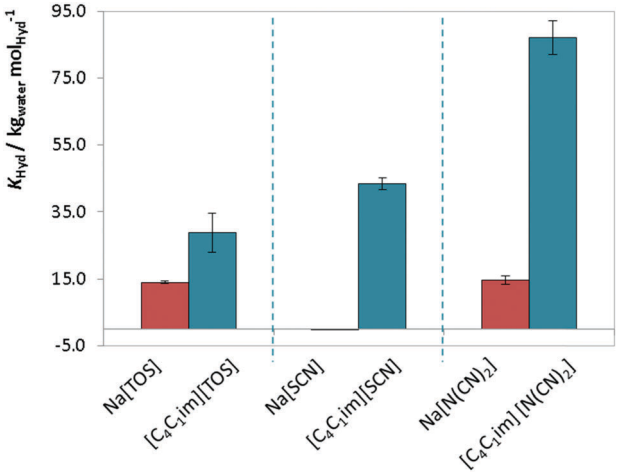

Fig. 5 K_{Hyd} values for ibuprofen using tosylate-, thiocyanate- and dicyanamide-based hydrotropes.

as depicted in Fig. 5. The replacement of a sodium cation (red bars) by an imidazolium cation (blue bars) leads to a remarkable enhancement in the solubility of ibuprofen.

To evaluate the influence of the IL anion on the solubility of ibuprofen, a series of $[C_4C_1im]$- and sodium-based hydrotropes were investigated. As previously mentioned, the conventional hydrotropes are usually anionic compounds composed of an aromatic ring substituted by an anionic group, such as a sulfate, sulfonate, or carboxylate group. Nevertheless, contrary to expectations, $[C_4C_1im][N(CN)_2]$ and $[C_4C_1im][SCN]$ presented even higher hydrotropic activity than $[C_4C_1im][TOS]$, as depicted in Fig. 6. Although dicyanamide and thiocyanate present an outstanding hydrotropic activity when conjugated with the $[C_4C_1im]^+$ cation, the same behaviour was not observed when these were combined with the sodium cation (Fig. 5). The results obtained support the idea that both anion and cation contribute to the hydrotropic mechanism in a synergistic manner, different from those previously observed.[32] The synergetic effect is confirmed by the MD simulation results discussed below.

In order to evaluate the formation of IL–ibuprofen aggregates, dynamic light scattering measurements were performed

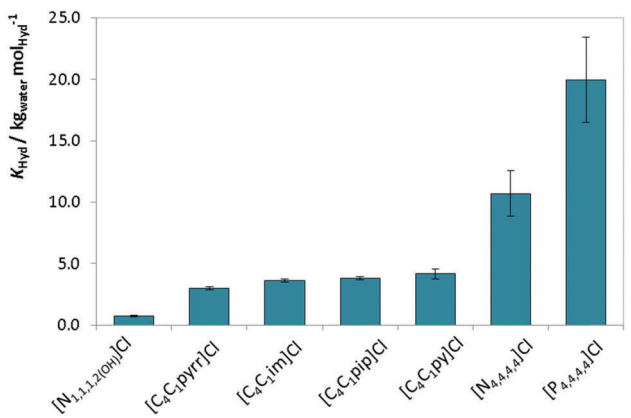

Fig. 4 K_{Hyd} values of the chloride-based ILs for ibuprofen.

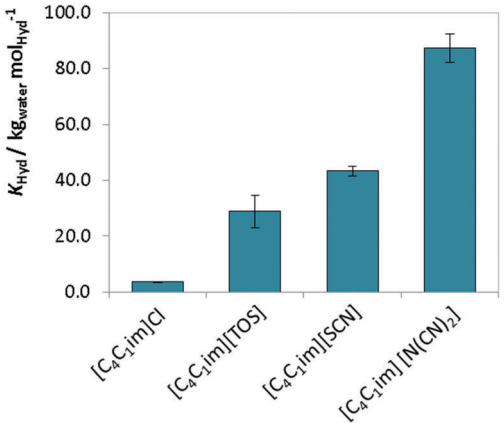

Fig. 6 K_{Hyd} values of the $[C_4C_1im]$-based ILs for ibuprofen.

for saturated solutions of ibuprofen in 2.5 mol kg^{-1} of the two best hydrotropes ([C_4C_1im][$N(CN)_2$] and [C_4C_1im][SCN]). The results obtained suggest the presence of co-aggregates between the ibuprofen and the IL ions in aqueous solution, with dimensions of 1–2 nm, as shown in Fig. S1 of the ESI.†

The phenomenon of polymorphism is quite common among organic molecules, and many drugs can crystallize into different polymorphic forms, including ibuprofen.[56,57] Thus, to evaluate the impact of the medium on the crystallization, suitable crystals of ibuprofen precipitated in ethanol and [C_4C_1im][SCN] solution were analysed by powder and single crystal X-ray diffraction and optical microscopy. The lattice parameters of the unit cell (a 14.5337(17) Å; b 7.8500(8) Å; c 10.5382 (13) Å; α 90°; β 99.533(4)°; γ 90°) were in agreement with its crystallographic data reported in the Cambridge Crystallographic Data Centre (see Fig. S2 in the ESI†). Although the same unit cell was observed, and no significant differences were identified in the power diffractogram (Fig. S2, ESI†), the crystals precipitated from the two media show different crystal habit with significant differences in the ibuprofen crystal morphology, as shown in ESI,† Fig. S3.[58,59] When the crystallization is carried out in ethanol, plate-shaped crystals were observed, as well as some tube-shaped crystals with the solvent evaporation. On the other hand, when ibuprofen is precipitated from the aqueous solution of [C_4C_1im][SCN], needle- and plate-shaped crystals were obtained.

Molecular dynamics simulations

Since the best results on the hydrotropic solubilization of ibuprofen were achieved with [C_4C_1im][$N(CN)_2$] and [C_4C_1im][SCN], these compounds were selected to carry out the MD simulations aimed at understanding the molecular mechanism of hydrotropic solubilization, and the role of the cation and anion in the process.

Hydrotropic phenomena occurring in IL aqueous solutions have been previously probed from a microscopic perspective using molecular dynamics simulations.[32] The MD results confirmed the existence of co-aggregates between the hydrophobic solute and the IL ions in aqueous solution and have shown that in the case of IL aqueous solutions containing vanillin, the hydrotrope effect was achieved *via* the synergy between specific vanillin–cation, cation–anion and anion–water interactions. The goal of the present MD study is to confirm if those mechanisms are still valid for poorly water-soluble substances like ibuprofen. All simulations were performed using ibuprofen as the solute. The very low solubility of ibuprofen posed important obstacles to the correct implementation of the simulation runs: even in cases where the solubility of ibuprofen in IL aqueous solutions is 100 times greater than that in pure water, the corresponding ibuprofen concentrations are still very small (10–30 mM solutions). This means that either the simulation boxes have adequate sizes but there are too few solute molecules, or the number of solute molecules is adequate but the boxes are too big and the simulations will take too long. This was not an issue in the previous MD study involving vanillin solutes since the solubility of vanillin in pure water is larger than the hydrotrope-enhanced solubility of ibuprofen in IL aqueous solutions.[32] Since the study of co-aggregates in solutions with just one (or very few) solute molecules is a *non-sequitur*, we have decided to perform the simulations in conditions well above the solubility limit of ibuprofen in water. This means that, unlike the vanillin case, we will not be able to compare undissolved and dissolved solute (in pure water and IL aqueous solutions, respectively) but rather undissolved ibuprofen interacting in the two types of media.

Fig. 7 shows three simulation snapshots corresponding to ibuprofen in pure water (panel A) and ibuprofen in [C_4C_1im]-[$N(CN)_2$] (panel B) and [C_4C_1im][SCN] (panel C) aqueous solutions (1 M IL concentrations). The ibuprofen concentration is 1.2 M in pure water and 1 M in the IL aqueous solutions. In all cases, the ibuprofen occupies an important part of the simulation box (20% in volume) and, as expected, the two-phase nature of the system is evident. Aggregation analyses (small graph insets in each panel) quantify such state of affairs: all ibuprofen molecules remain aggregated to each other even when in contact with the IL aqueous solutions. Although this implies that in terms of solubilisation of the ibuprofen molecules nothing significant is happening—the amount of water-rich phases is simply too small to see any difference between pure water and the IL aqueous solutions in terms of their saturation by ibuprofen molecules—this does not mean that the molecular mechanisms responsible for the hydrotrope effects are absent in the IL aqueous solutions. In fact, the

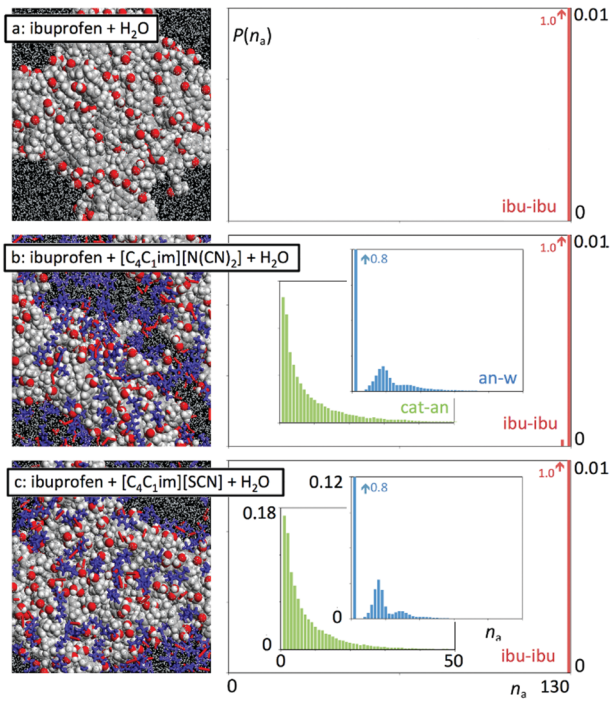

Fig. 7 Simulation snapshots and discrete probability distribution functions of aggregate sizes, $P(n_a)$, for ibuprofen in pure water (a) and in aqueous solutions of [C_4C_1im][$N(CN)_2$] (b) and [C_4C_1im][SCN] (c). The snapshots depict ibuprofen as space-filled molecules in CPK colors; water molecules as white dots and ionic liquid ions as blue (cation) and red (anion) wireframes. The histogram functions correspond to ibuprofen clusters (red bars), the anion–water network (blue) and the ionic liquid polar aggregates (green).

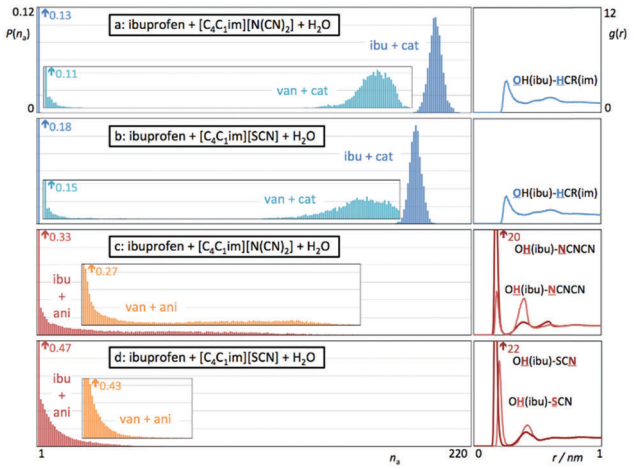

Fig. 8 Discrete probability distribution functions of aggregate sizes, $P(n_a)$, and pair radial distribution functions, $g(r)$, for different types of aggregates and interaction centres. (a and b) Cation–ibuprofen aggregates and interactions in systems with dicyanamide- (a) and thiocyanate-based ILs (b). (c and d) Anion–ibuprofen aggregates and interactions in systems with dicyanamide- (c) and thiocyanate-based ILs (d).

ibuprofen molecules are sensitive to the media where they are immersed, as attested by the orientation of the hydroxyl groups of the ibuprofen molecules at the surface of the ibuprofen sub-phase towards the aqueous sub-phase.

Fig. 8 shows aggregate analyses between the ions of the IL present in the IL aqueous solutions and the ibuprofen molecules. These analyses are complemented by radial distribution functions (RDFs) between selected sites in the ions (most acidic hydrogen atoms in the imidazolium cation, HCR; nitrogen or sulfur atoms in the anions) and in the ibuprofen molecule (oxygen and hydrogen atoms of the hydroxyl group). The results show that there are important interactions between the IL ions and the ibuprofen molecules and an extensive network formed by the ions (mainly the cations) and the ibuprofen molecules at the surface of the ibuprofen sub-phase.

Actually, the aggregation patterns shown between the ibuprofen molecules and the IL ions are very similar to those found between the same ions and the vanillin molecules in a previous study[32] (for comparison purposes we have also included the corresponding graphs in Fig. 8). This means that the molecular mechanisms responsible for the hydrotrope effect are already in place even for molecules with extremely low water solubility: the IL ions are already being used as interaction mediators between the two sub-phases present in the system.

The big difference between the vanillin and ibuprofen systems in the concentration ranges analyzed by MD is that in the former case such interactions are sufficient to overcome the interactions between the (smaller) vanillin molecules, whereas in the latter case the stronger interactions between the larger hydrocarbon moieties of ibuprofen prevent such outcome. In other words, if simulations with ibuprofen solutions 100 times more diluted were performed (simulation boxes with 100 times more aqueous subphase) one would see dissolution patterns in pure water and in the IL aqueous solutions similar to those already witnessed for vanillin at much higher concentrations.

As already stated, such big simulations are not possible in terms of acceptable periods of time—time in a MD simulation scales with the square of the number of particles. Nevertheless, we have decided to perform simulations with similar box sizes but only 10 ibuprofen molecules (a 10-fold dilution in relation to the already described simulations) to check possible dissolution trends in a semi-quantitative way (statistics with just ten solute particles are poor and aggregation analyses are obviously very limited). The results, presented in Fig. 9, show the partial dissolution of the ibuprofen subphase when pure water is replaced by an IL aqueous subphase. The ibuprofen aggregation patterns (very limited in this case) shift accordingly from larger aggregates to smaller ones and suggest that the hydrotrope effect is stronger for the dicyanamide-based systems relative to the thiocyanate-based ones.

The general character of the molecular mechanism underlying the hydrotrope effect revealed by the MD simulations (ILs as interaction mediators between organic and aqueous subphases without the need of invoking self-organized structures such as those found in surfactant systems) helps rationalize the experimental results obtained in the present work with other solute–IL combinations. On the side of the organic subphase,

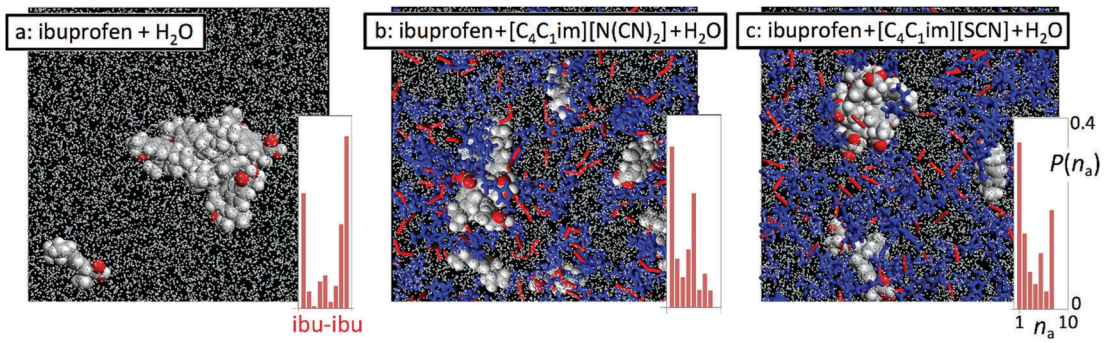

Fig. 9 Simulation snapshots and discrete probability distribution functions of aggregate sizes, $P(n_a)$, for ibuprofen in pure water (a) and in aqueous solutions of $[C_4C_1im][N(CN)_2]$ (b) and $[C_4C_1im][SCN]$ (c). The snapshots depict ibuprofen as space-filled molecules in CPK colours; water molecules as white dots and IL ions as blue (cation) and red (anion) wireframes. The histogram functions correspond to ibuprofen clusters (red bars).

cations or anions with larger non-polar moieties (*e.g.* ammonium or phosphonium cations) enhance the hydrotrope effect due to stronger dispersive forces with the solute. It is interesting to note that such non-polar moieties can originate from either the anion or cation, which may account for the synergistic effects witnessed in many ion combinations. On the aqueous sub-phase side, ions that are able to interact with both their counter-ion and the water molecules simultaneously are better hydrotropes. Halides are not as efficient as dicyanamide or thiocyanate anions and sodium is less efficient than most IL cations because they are solvated too strongly by water and are less prone to interact with their counter-ions in aqueous solution.

Conclusion

The results reported in this work clearly evidence the outstanding ability of ILs to act as hydrotropes for ibuprofen. Furthermore, the cation and anion may synergistically contribute to the hydrotropic mechanism of solubilization, which makes them powerful catanionic hydrotropes. Considering the chloride-based IL series, the $[N_{4,4,4,4}]Cl$ and $[P_{4,4,4,4}]Cl$ have presented a higher increase in the solubility of ibuprofen. On the other hand, considering the 1-butyl-3-methylimidazolium family, dicyanamide and thiocyanate anions were the best hydrotropic solubilizing agents where this cation–anion synergy was more evident. As previously observed for vanillin, the results obtained using MD simulation support the idea that the hydrotropic phenomenon of the ILs for ibuprofen is driven by the formation of drug–IL aggregates.

Conflicts of interest

There are no conflicts to declare.

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