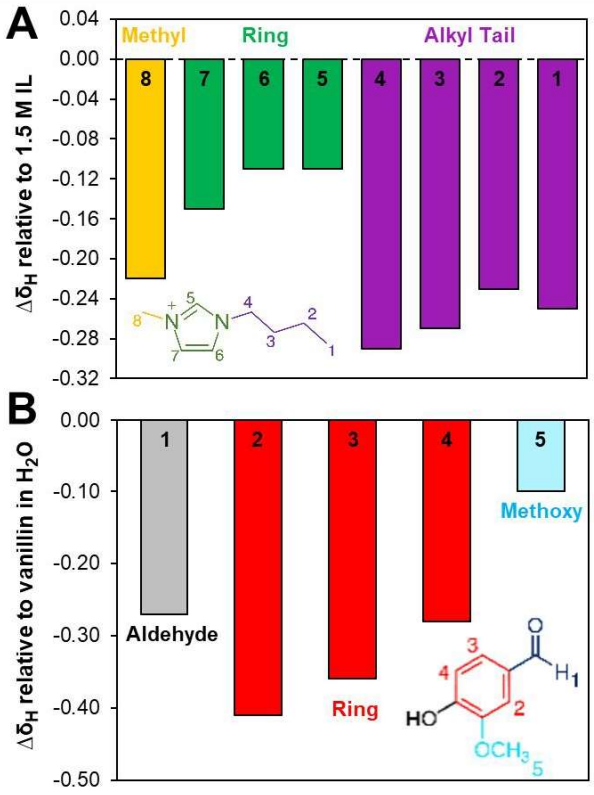

Figure 3. A) Proton chemical shifts ($\Delta\delta_H$) of the IL cation in a 1.5 M solution of [C_4mim]Cl in water, saturated with vanillin, relative to an aqueous 1.5 M IL solution with no solute. B) Vanillin molecule in saturated aqueous 1.5 M IL solution relative to vanillin dissolved in water to saturation.

In the case of both hydrotrope and solute, a clear site-specificity in the locus of interaction is observed manifested by the different $\Delta\delta_H$ values for each proton. A negative $\Delta\delta_H$ indicates that the immediate proton environment is more shielded as water is replaced from its coordination sphere by a more apolar group. There is a clear distinction between the change in environment of the IL ring with a delocalised charge and the more hydrophobic butyl chain in the presence of a solute. Whilst the smaller $\Delta\delta_H$ of the ring protons suggests these remain primarily hydrated, the addition of vanillin provided a significant shielding for all hydrogens of the hydrocarbon tail and suggests a preferred tail-solute interaction over a ring-solute one. When comparing vanillin dissolved to saturation in 1.5 M IL aqueous solution to vanillin in water (**Figure 3B**), all solute hydrogens are more shielded in the presence of hydrotrope. This effect is especially pronounced for the aromatic hydrogens H2 and H3 of the ring, see **Figure 3B** for hydrogen labelling. In contrast, the hydrogens closest to the more hydrophilic hydroxyl (H4), aldehyde (H1) and methoxy (H5) groups present the smallest $\Delta\delta_H$ as these groups are less prone to interact with the hydrotrope. The $\Delta\delta_H$ in **Figure 3** suggests that the significant increased vanillin solubility in 1.5 M IL solutions occurs through the displacement of water molecules

around the aromatic ring of the solute by the alkyl chain segment of the hydrotrope, its most hydrophobic sites, thus revealing favoured hydrophobic hydrotrope-solute interactions. This is consistent with the emergence of aggregates with an average hydrodynamic diameter of 2.01 nm, as measured by DLS (**Figure S2**), whilst no aggregates were observed in aqueous [C_4mim]Cl solution (detection limit of 0.70 nm). This evidenced hydrophobic interaction is in support of the hydrotropy model proposed by Shimizu *et al*.[14] The hydrotropic solubilisation mechanism is induced by the accumulation of the hydrotrope around the solute and the formation of hydrotrope-solute aggregates where the apolar moieties are associated while the polar moieties are kept mostly in contact with water. The ^{1}H-NMR results in **Figure 3** confirm that the interaction between an hydrotrope and solute is site-specific, as significant interaction site selectivity is observed. This provides a partial explanation as to the higher solubilisation selectivity of hydrotropes when compared with surfactants and reinforces the difference between the two categories.

Hydrotrope interaction in presence of a salt

Aqueous solutions of 1.5 M IL doped with a fixed concentration of 1.0 M of individual salts without the vanillin solute were investigated by NMR and DLS with the results presented in **Figure 4**. Due to the similar qualitative behaviour of the ^{1}H-NMR shifts for the IL cation hydrogens the discussion will focus on the $\Delta\delta_H$ of the alkyl tail terminal CH_3 group although, as observed in **Figure 3A**, the cationic butyl chain always tends to have a less electronegative environment than the imidazolium ring. The addition of an inorganic salt resulted in a shielding of all hydrogens relative to the aqueous IL solution. The magnitude of the induced $\Delta\delta_H$ follows the sequence $Y^{3+} > Ca^{2+} > Na^+ > Li^+$ and correlates well with the salting-out extent of each salt represented by their respective surface tension increment, **Figure 4A**. More importantly, a comparison of the induced $\Delta\delta_H$ and the average IL aggregate diameter in each salt solution in **Figure 4B** confirms that $\Delta\delta_H$ is indicative of enhanced IL-IL interaction. The DLS profiles for the 1.5 M IL + 1.0 M salt solutions are presented in **Figure S3** with the average hydrodynamic diameter increasing from Li^+ (0.82 nm) < Na^+ (0.93 nm) < Ca^{2+} (1.09 nm) < Y^{3+} (1.48 nm). It must be emphasised that these aggregates were polydisperse and do not correspond to any organised structures such as micelles.[44] Ultimately, the increased IL-IL interaction and dehydration in the presence of chloride salts in the absence of solute negatively affects its hydrotropic capacity as reflected by the decreasing $K_{IL+Salt}$ at 1.5 M IL with $\Delta\delta_H$ shown in **Figure 4C**. This further accentuates that the decrease in vanillin solubility in the ternary system is partially determined by the aggregation (salting-out) of the IL component and not solely of the solute as could be expected.

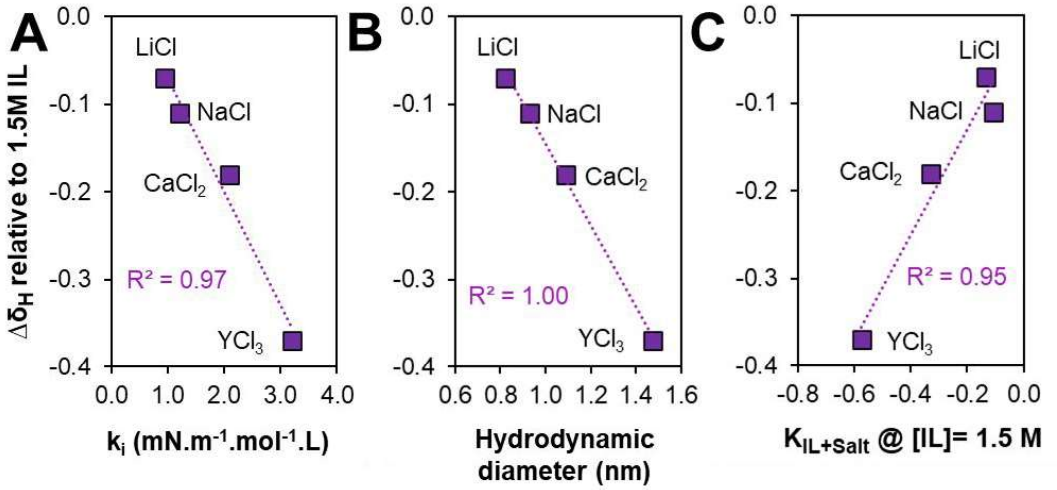

Figure 4. Correlation between the average $\Delta\delta_H$ of an aqueous 1.5 M IL after and before the addition of 1.0 M of chloride salt (no solute) to A) the surface tension increment of each salt, B) diameter of the IL aggregates in solution and C) the $K_{IL+Salt}$ of the respective salt at 1.5 M IL.

Hydrotrope-solute interactions in the presence of a salt

Finally, 1.5 M [C_4mim]Cl solutions containing 1.0 M of NaCl, $CaCl_2$ or YCl_3 and saturated with vanillin were investigated, with the $\Delta\delta_H$ relative to the salt solutions without solute presented in **Figure 5A**. No clear trends emerge in relation to the salt valency, with the magnitude of $\Delta\delta_H$ in **Figure 5A** indicating an inverse cation organizational series of Ca^{2+} > Na^+ > Y^{3+} for the IL imidazolium head hydrogens and Ca^{2+} > Y^{3+} > Na^+ for the methyl and butyl groups hydrogens in the ternary system with solute relative to the IL + salt system in **Figure 4**. This inversion in tendency between the binary and ternary system suggests that the formation of more apolar aggregates is primarily determined by the salting-out influence in the case of the higher charge density cation Y^{3+}. In contrast, the increased hydrogen shielding of the IL in the 1.5M IL + vanillin + 1.0 M $CaCl_2$, and to a lesser extent the NaCl system, can be attributed to the introduction of vanillin and not to the salt This observation reinforces that hydrotropic solubilisation occurs preferentially through a tail-solute hydrophobic interaction over a ring-solute one. The site-specificity in the immediate environment of the IL cation is preserved in the ternary systems containing Ca^{2+} and Y^{3+}, with the butyl chain hydrogens presenting more negative $\Delta\delta_H$ values when compared to the imidazolium head. In contrast, the ternary system containing Na^+ presents an inverse tendency with $\Delta\delta_H$ values with the exception of the H(4) hydrogens which appear as outliers. The NaCl salt induces shielding in every hydrogen of the IL cation. This is in sharp contrast to the specificity observed in the binary system of IL and solute in the absence of inorganic salts shown in **Figure 3A** although the justification as to this is unclear.

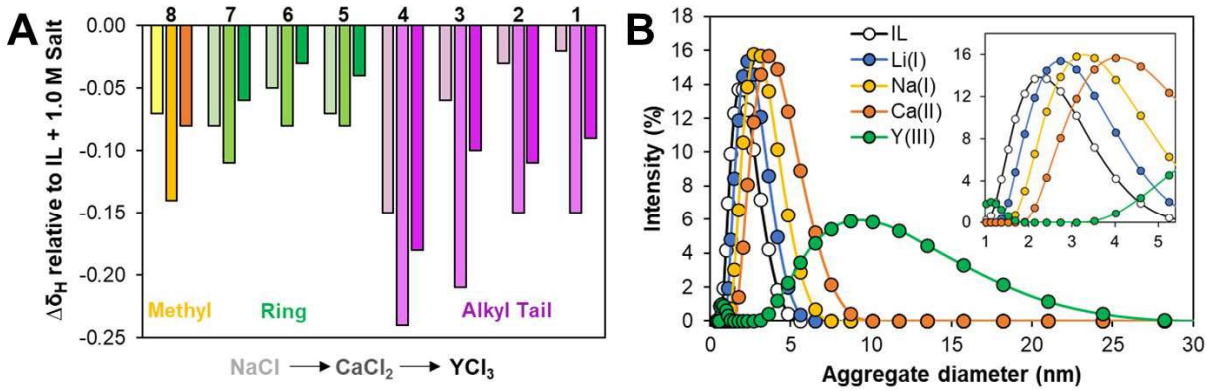

Figure 5. A) $\Delta\delta_H$ of the $[C_4mim]^+$ cationic hydrogen in the ternary system of IL + vanillin + salt relative to the binary IL + salt system for a fixed IL and salt concentration of 1.5 and 1.0 M respectively. Peak labelling corresponds to those in **Figure 3A**. B) Aggregate size distribution by intensity obtained by DLS in 1.5 M $[C_4mim]Cl$ aqueous solutions saturated with vanillin and doped with 1.0 M of inorganic chloride salts.

The same solutions in **Figure 5A** were analysed by DLS to detect eventual aggregate formation with the diameters presented in **Figure 5B**. The results support the link between decreased solubility via salt addition and the formation of aggregates of increasing size. The smallest aggregate diameters were obtained for the binary IL+vanillin system (distribution centred at 2.01 nm) whilst the ternary IL+vanillin+YCl_3 system yielded a large aggregate distribution with a maximum at approximately 10.16 nm. Aggregates in the LiCl, NaCl and $CaCl_2$ systems present a partially overlapping distribution with the distribution maximum shifting from 2.48 nm for LiCl, 3.05 nm for NaCl and 3.91 nm for $CaCl_2$. The formation of consistently bigger aggregates along the $Li^+ < Na^+ < Ca^{2+} < Y^{3+}$ series results from increases in the hydrotrope-hydrotrope interactions. With this promoted IL aggregation there are fewer IL cations available to take part in the hydrotropic solubilization of vanillin, which justifies the decreased solubility observed in the hydrotropic solubility measurements presented earlier. The smaller aggregate size in aqueous IL solutions doped with salt in contrast with the aggregates observed in the present analysis reinforces the understanding that the presence of solute is essential as a nucleation point for significant aggregation to happen around it, and thus to the hydrotropic effect.

Statistical thermodynamic rationalisation

The Setschenow constant is linked to the Kirkwood-Buff integrals (KBI) through a series of pair-wise interaction parameters.[45,46] In this section and the associated Appendix, the notation was modified

from that used in equation (1) to be consistent with previous derivations[14–18] and generalise the discussion to any hydrotrope-salt-solute system. For a solute (S) in equilibrium with its pure phase and at any concentration, rigorous statistical thermodynamic theory of hydrotropy by Shimizu and colleagues can be extended to expresses the hydrotropic solubilization in the presence of salts and account for the hydrotrope (H), salt (A), and water (W) present in the system according to the equation below:

$$kT\left(\frac{\partial \ln c_S}{\partial c_H}\right)_{T,P,c_A;\mu_S=\mu_S^0} = \left[c_H(G_{S,H}-G_{S,W}) - \frac{c_H c_A(G_{S,A}-G_{S,W})(G_{H,A}-G_{A,W})}{1+c_A(G_{A,A}-G_{A,W})}\right]\left(\frac{\partial \mu_H}{\partial c_H}\right)_{T,P,c_A;\mu_S=\mu_S^0} \quad \text{- (2)}$$

where $G_{i,j}$ represents the KBI between the component *i* and *j*, μ_i is the chemical potential of the species i and $c_i = \langle N_i \rangle / V$ is the bulk number density of the species i, respectively. A detailed derivation of equation (2) is available in the Appendix.

A qualitative rationalisation of the experimental results is proposed below based on the change in the individual term contribution of equation (2) upon salt addition. Statistical thermodynamics shows that hydrotropic solubilization is mainly driven by solute-hydrotrope preferential interactions relative to solute-water, making $(G_{S,H} - G_{S,W}) > 0$ the primary contribution for solubilisation.[14–18] Any loss in site-specificity, i.e., the loss of the prevalent hydrophobic hydrotrope-solute interactions in **Figure 3**, driven by changes in the hydrotrope or salt concentrations can decrease this term. In the present work, a third component is introduced in a hydrotropic solution/solute system. Let us look at the impact of each term on Eq. (2):

(a) The $(G_{S,A} - G_{S,W})$ factor: The unfavourable solute-salt interaction implies that $(G_{S,A} - G_{S,W}) < 0$ and reduces solubilisation as shown in **Figure 1C** and is dependent on the salt concentration. Note that only the chloride anion was assessed, and the above statement should be revisited in the presence of salts with salting-in anions.

(b) The $(G_{H,A} - G_{A,W})$ factor: Salt-water interaction is preferential to hydrotrope-salt interaction as a consequence of hydrotrope-hydrotrope interaction as clearly shown by the results in **Figure 4**, making $(G_{H,A} - G_{A,W}) < 0$.

(c) The $1 + c_A(G_{A,A} - G_{A,W})$ factor: The self-association of salt preferential to salt-water association causes the deviation from 1 of the denominator but does not affect the sign of the second term in the bracket.

(d) The $\left(\frac{\partial \mu_H}{\partial c_H}\right)_{T,P,c_A;\mu_S}$ factor: This factor is positive as expected when considering the binary IL+vanillin system solubility curve[11] but reduced by the hydrotrope self-association enhanced by the addition of salt.

From this analysis, two aspects contribute to the reduction of hydrotropic solubilization due to hydrotrope self-association enhanced by the addition of salt: (i) the negative overall second term in the bracket in equation (2) as can be concluded from (a)-(d) and (ii) the decrease in the $\left(\frac{\partial \mu_H}{\partial c_H}\right)_{T,P,c_A;\mu_S}$ term.

CONCLUSIONS

In this work, the solubility of vanillin in the aqueous solutions of the hydrotrope [C_4mim]Cl in the presence of inorganic chloride salts of varying valency was investigated. It was found that the addition of salt resulted in a reduced vanillin solubility, this reduction correlating with the surface tension increment induced by the salt. The results presented support the mechanism of hydrotropy proposed by Shimizu and colleagues based on statistical thermodynamics, with hydrotropic solubilization found to be linked with hydrotrope and solute aggregation and driven mainly by hydrophobic interactions. Site specificity of hydrotrope-solute interactions was evidenced and seen to be dampened by the addition of salt. The addition of inorganic salts promotes IL-IL interaction even in the absence of vanillin and ultimately the formation of larger solute-hydrotrope aggregates. The formation of IL-IL aggregates hindered vanillin solubility, suggesting that pre-clustering of the hydrotrope is not beneficial towards hydrotropy. The particularities of solubilization behaviour in salted environments may have interesting and creative biological applications, since different *in vivo* locations possess different electrolyte environments. Only the cationic component was evaluated in this work that must be extended in a future work to the anionic contribution as the latter are known to exert a greater influence on the salting-in/out of the system.

APPENDIX

Under constant temperature and pressure, the chemical potential of a solute, μ_S^*, whose centre-of-mass is fixed at origin, can be expressed as

$$-d\mu_S^* = \sum_{i=W,H,A,S} \left(\langle N_i \rangle_S - \langle N_i \rangle\right) d\mu_i \tag{A.1}$$

where μ_i is the chemical potential of the species i. $\langle N_i \rangle_S$ and $\langle N_i \rangle$ express the ensemble average of the numbers of the species i in the presence and absence of a fixed solute, respectively.[17,46] The notation adopted here is consistent with "Statistical thermodynamic rationalisation" section of this paper. Using the definition of the Kirkwood-Buff integral,

$$c_i G_{S,i} = \langle N_i \rangle_S - \langle N_i \rangle \tag{A.2}$$

Using Eq. (A.2), Eq. (A.1) is rewritten as

$$-d\mu_S^* = \sum_{i=W,H,A,S} c_i G_{S,i} d\mu_i \tag{A.3}$$

where $c_i = \langle N_j \rangle / V$ is the bulk number density of the species i.

To express how the solvation free energy of a solute, μ_S^*, is affected by the addition of a hydrotrope, the Gibbs-Duhem equation under constant T and P is used:[17,47]

$$0 = \sum_{i=W,H,A,S} c_i d\mu_i \tag{A.4}$$

Eliminating $d\mu_W$ from Eq. (A.3) using Eq. (A.4) yields

$$-d\mu_S^* = \sum_{i=H,A,S} c_i (G_{S,i} - G_{S,W})\, d\mu_i \tag{A.5}$$

We then consider an equilibrium between a solute in its pure phase μ_S^o and in solution μ_S. Since μ_S^o only depends on T and P, $\mu_S = \mu_S^o$ is a constant. Therefore,

$$d\mu_S = 0 \tag{A.6}$$

Because of Eq. (A.6), the solute-solute KBI (i.e., the last term of Eq. (A.5)) does not affect solubilization. Note that the solute-solute correlations affect $d\mu_S^*$ indirectly by modifying $G_{S,W}$, $G_{S,H}$ and $G_{S,A}$. We also use the well-known relationship between μ_S^* and μ_S,[47]

$$d\mu_S = d\mu_S^* + kTd\ln c_S \tag{A.7}$$

Combining Eqs. (A.5)–(A.7), the following relationship is obtained:

$$kTd\ln c_S = c_H(G_{S,H} - G_{S,W})d\mu_H + c_A(G_{S,A} - G_{S,W})d\mu_A \tag{A.8}$$

Here Eq. (2) of the main article is derived, i.e., solubilization by hydrotrope under a constant salt concentration. Differentiating Eq. (A.8) with respect to c_H under constant c_A yields

$$kT\left(\frac{\partial \ln c_S}{\partial c_H}\right)_{T,c_A,P;\mu_S=\mu_S^o} = c_H(G_{S,H} - G_{S,W})\left(\frac{\partial \mu_H}{\partial c_H}\right)_{T,c_A,P;\mu_S=\mu_S^o} + c_A(G_{S,A} - G_{S,W})\left(\frac{\partial \mu_A}{\partial c_H}\right)_{T,c_A,P;\mu_S=\mu_S^o} \tag{A.9}$$

We again use Eqs. (A.1) and (A.3), this time with a fixed A instead of a fixed S, to eliminate $\left(\frac{\partial \mu_A}{\partial c_H}\right)_{T,c_A,P;\mu_S=\mu_S^0}$. Using Eq. (A.7) for a fixed A, eliminating $d\mu_W$ using Eq. (A.4), and under phase equilibrium (Eq. (A.6)), we obtain

$$kT\frac{dc_A}{c_A} = [1 + c_A(G_{A,A} - G_{A,W})]d\mu_A + c_H(G_{H,A} - G_{A,W})d\mu_H \tag{A.10}$$

Under constant c_A, Eq. (A.10) leads to

$$0 = [1 + c_A(G_{A,A} - G_{A,W})]\left(\frac{\partial \mu_A}{\partial c_H}\right)_{T,P,c_A;\mu_S=\mu_S^0} + c_H(G_{H,A} - G_{A,W})\left(\frac{\partial \mu_H}{\partial c_H}\right)_{T,P,c_A;\mu_S=\mu_S^0} \tag{A.11}$$

Combining Eqs. (A.9) and (A.11) leads to Eq. (2) of the main text.

Conflicts of interest

There are no conflicts to declare.

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