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The Impact of the Counterion in the Performance of Ionic Hydrotropes

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The efficiency of an ionic hydrotrope is shown to increase with the hydrophobicity of its counterion, challenging the common view that ionic hydrotropes should possess a small, densely charged counterion such as sodium or chloride.

Hydrotropy is a powerful approach to enhance the aqueous solubility of hydrophobic solutes by the addition of a third component, the hydrotrope, which is a small, amphiphilic molecule that favourably interacts with both water and hydrophobic molecules.[1–5] The chief difference between a surfactant and a hydrotrope is the inability of the latter to self-aggregate into micellar structures in the bulk solution phase due to its small size. A few examples of classical hydrotropes include non-ionic compounds such as urea, chloride-based salts such as toluidine hydrochloride, and sodium-based salts such as sodium p-toluenesulfonate.[1–8] The ability of hydrotropy to increase the aqueous solubility of hydrophobic compounds drastically expands the range of chemical processes where water, the greenest of solvents, can be used efficiently. Thus, hydrotropy is aligned with the principles of green chemistry and is an important tool in the ongoing search for more sustainable solvents that would mitigate the problems associated to classical volatile organic solvents.[9,10]

The solubilizing power of ionic hydrotropes has been attributed to their highly hydrophilic counterions. In fact, sodium and chloride-based salts have been the common choice of hydrotropes in the literature,[1–8] with some authors even defining ionic hydrotropes as salts composed of one amphiphilic ion and one very hydrophilic counterion.[1] This view, however, needs to be re-examined in light of recent developments in the mechanism of hydrotropy, which suggests that the presence of hydrophilic ions may have a negative impact on the efficiency of a hydrotrope, as explained below.

Hydrotropy occurs due to the water-mediated aggregation of hydrotrope molecules around the hydrophobic solute.[11–13] In brief, apolar surfaces are forced to aggregate in aqueous solutions to minimize the disruption of the hydrogen bond network of water (hydrophobic effect). Thus, hydrotropes work by aggregating around hydrophobic solutes through their apolar moieties, while retaining relevant interactions with water through their hydrophilic moieties, hence the importance of their amphiphilicity. In the case of ionic hydrotropes, the movement of the counterion into the vicinity of hydrotrope-solute aggregates minimizes their local charge which increases their stability. In turn, this leads to larger aggregates and a greater solubility enhancement of the solute. This effect cannot be obtained easily using hydrophilic counterions since their strong solvation shells with water limit the extension of their interaction with the aggregates.

The objective of this work is to challenge the current consensus that ionic hydrotropes need a highly hydrophilic counterion by systematically comparing the influence of its apolarity in the performance of ionic hydrotropes. First, it will be shown that hydrotropes composed of two amphiphilic ions are superior to hydrotropes containing a small, densely charged counterion. Then, it will be shown, for highly hydrophobic solutes (naproxen and ibuprofen), that the best counterion is intimately related to the Hofmeister series, with counterions such as dicyanamide and thiocyanate excelling at increasing the solubility of the solutes. Both results play a key role in explaining recent works that suggest that ionic liquids may perform better than classical hydrotropes.[14,15]

To probe the impact of the apolarity of the counterion, the solubility enhancement of several solutes with varying degrees of hydrophobicity (caffeine, gallic acid, vanillin, syringic acid, naproxen, and ibuprofen; their octanol-water partition coefficients are reported below) was measured in this work (section S1 of the ESI) in the presence of Na[TOS], [C_4C_1im]Cl, and [C_4C_1im][TOS] (see Table S1 for abbreviations). These results are reported in Figure 1 and Tables S2-S8 of the ESI. The aqueous solubility enhancement of all solutes was measured in

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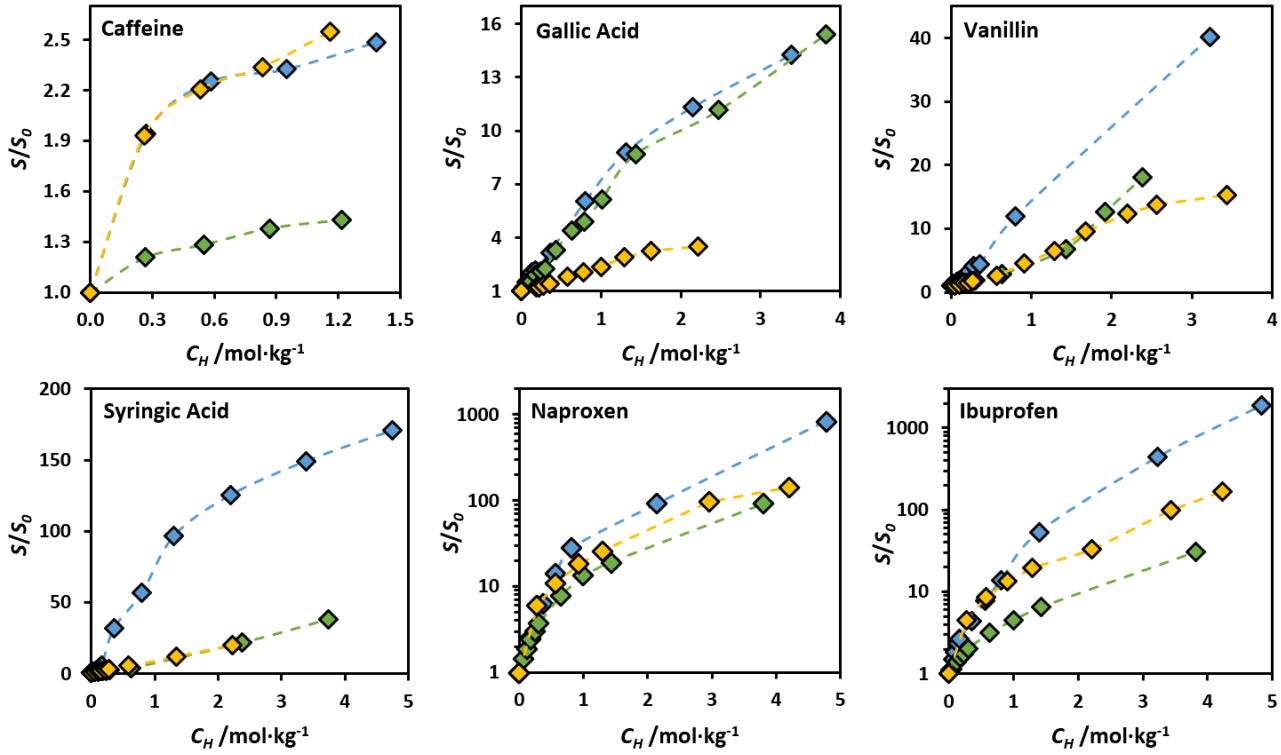

Figure 1. Aqueous solubility enhancement (S/S_0) of several solutes as a function of the molal concentration (solute-free basis) of [C_4C_1im][TOS] (◆),[C_4C_1im]Cl (◆), or Na[TOS] (◆), at 303.2 K. Data measured in this work (section S1 of ESI) or taken from the literature.[14,15]

the concentration range from pure water up to a hydrotrope concentration of about 4 mol·kg^{-1}.

Figure 1 reveals that [C_4C_1im][TOS] is the best hydrotrope for all solutes in the concentration range studied, except for caffeine where [C_4C_1im][TOS] and Na[TOS] provide roughly the same solubility enhancement, confirming that the use of an amphiphilic counterion, rather than the prototypical sodium and chloride ions, favors the solubility enhancement of hydrophobic solutes. In line with previous works,[16,17] the efficiency of the hydrotropes generally increases as the hydrophobicity of the solute increases, which can be quantified by the logarithm of its octanol/water partition coefficient (caffeine – -0.07, gallic acid – 0.7, vanillin – 1.37, syringic acid – 1.04, naproxen – 3.18, ibuprofen – 3.97).[18] This results in astonishing 1000-fold solubility enhancements for the most hydrophobic solutes (naproxen and ibuprofen).

The solubility data reported in Figure 1 were fitted using the cooperative model of hydrotropy developed by Shimizu and Matubayasi[12] (section S2 of the ESI). The fitted curves were used to show that the solubility enhancement due to the presence of [C_4C_1im][TOS] is not simply the sum of the solubility enhancements provided by [C_4C_1im]Cl and Na[TOS], with Figure S7 showing that the former is greater than the latter for the most hydrophobic solutes studied (vanillin, syringic acid, naproxen, and ibuprofen). This can be rationalized by considering that (i) a synergistic effect exists between large amphiphilic ions, such as [C_4C_1im] and [TOS], or (ii) small, densely charged ions, such as sodium and chloride, negatively impact the performance of a hydrotrope. Both scenarios are in line with the water-mediated aggregation mechanism proposed for hydrotropy, as explained below.

In the case of classical ionic hydrotropes, such as Na[TOS], only one of the ions bears apolar moieties able to aggregate around the solute due to the hydrophobic effect. Because the counterion is small and densely charged, it preferentially interacts with water, forming a strong solvation shell. However, the formation of solute-hydrotrope aggregates depends on the aggregation of the bulky ion around the solute as well as the movement of the counterion into the vicinity of the solute to maintain charge neutrality. The dehydration of the counterion from the bulk solution into the vicinity of the solute-hydrotrope cluster is favored by its apolarity. Thus, the superiority of [C_4C_1im][TOS] as a hydrotrope over [C_4C_1im]Cl or Na[TOS] becomes apparent. Unlike the other two salts, both ions of [C_4C_1im][TOS] are bulky and do not form strong solvation structures with water. Thus, they can easily be driven to aggregate around the solute through their apolar moieties, and there is no counterion with strong interactions with water limiting the extent of solute-hydrotrope aggregation. This also explains why ionic liquids are excellent hydrotropes, as previously reported in the literature.[14,15] By their very nature, ionic liquids possess bulky ions that are not densely charged. Thus, both of their ions can be driven to aggregate around the solute through their apolar moieties allowing for larger solute-hydrotrope aggregates and, thus, larger solubility enhancements.

The results presented so far reveal why [C_4C_1im][TOS] becomes a more effective solubilizer than [C_4C_1im]Cl or Na[TOS] as the hydrophobicity of the solute increases (Figure S7).

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Because the number of ions that need to aggregate around the solute to enhance its solubility increases with its apolar volume, the excess charge of solute-hydrotrope aggregates is larger for more hydrophobic solutes. In turn, this requires a larger number of counterions in the vicinity of the aggregates to counter the excess local charge.

So far, experimental evidence in favor of using ionic hydrotropes that are comprised only of amphiphilic ions has been presented. Now, the impact of the counterions is investigated using the two most hydrophobic solutes studied in this work, i.e., the drugs ibuprofen and naproxen, where the choice of counterion appears to have a larger impact (Figure S7). As such, the aqueous solubility enhancement of naproxen and ibuprofen was measured (see section S1 of the ESI) in the presence of the hydrotropes [C_4C_1im][DCA] or [C_4C_1im][SCN] (see Table S1 for abbreviations). These results are reported in Tables S9-S10 of the ESI and depicted, along with the previous solubility results using [C_4C_1im]Cl and [C_4C_1im][TOS], in Figure 2.

Figure 2 reveals that [DCA] and [SCN] are better counterions than [TOS] which, in turn, is better than the chloride ion, when combined with [C_4C_1im] to enhance the aqueous solubility of naproxen and ibuprofen. The solubility differences provided by [DCA], [SCN], and [TOS] fade as the concentration of hydrotrope increases, but the trend is clear. In other words, the impact of the counterion in the solubility enhancement of the studied solutes can be ranked in the following manner: Cl < TOS < SCN< DCA. This is a rather interesting result considering its striking resemblance to the Hofmeister series of anions.

The counterion ranking found in this work for hydrotropy is commonplace across different solubility topics. For instance, Underwood and Anacker[19] studied the impact of the counterion in the critical micellar concentration (CMC) of decyltrimethylammonium-based surfactants and found that, among several common inorganic anions, thiocyanate led to the smaller CMC value, which was ten times smaller than the CMC value obtained using chloride. The ability of thiocyanate and dicyanamide to stabilize micelles is often rationalized by the low hydration energies of these ions.[19–22] In 2002, Leontidis[22] discussed this effect in the formation of micelles, and categorized anions such as thiocyanate as a class of counterions that do not hydrate easily or, in other words, are not surrounded by strong hydration shells, unlike sodium or chloride ions. This class of counterions is more readily available to form ion pairs with the surfactant, often leading to precipitation of the surfactant.

The results presented above clarify the connection between the Hofmeister series and hydrotropy, when the Hofmeister effect is also understood as the (water-mediated) interaction between an ion and a molecule, both in a specific and non-specific manner, rather than the modifier of the "water structure" as in the old view.[23,24] The movement of the counterion of an ionic hydrotrope from bulk solution into the vicinity of the solute-hydrotrope aggregate is favored by (i) the hydrophobic effect, which requires the counterion to have a large apolar volume to aggregate around the solute or (ii) small hydration energies, which decrease counterion-water

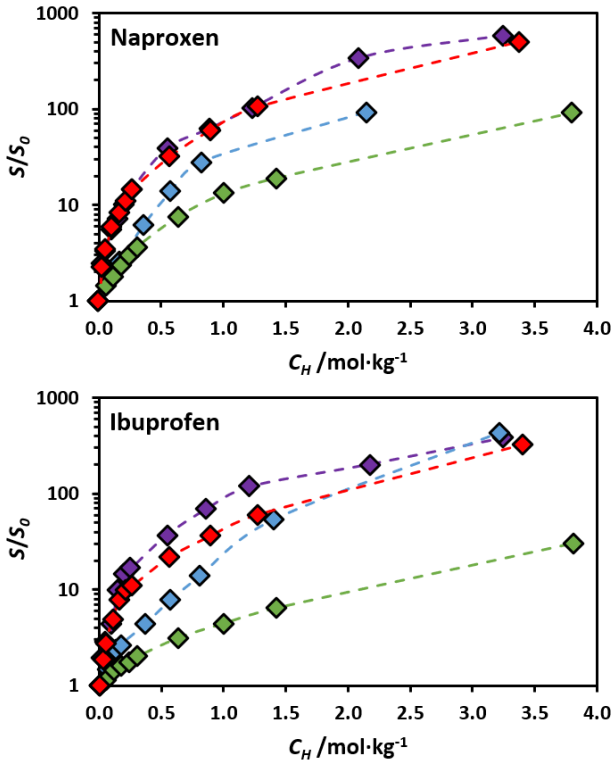

Figure 2. Aqueous solubility enhancement (S/S_0) of naproxen and ibuprofen as a function of the molal concentration (solute-free basis) of [C_4C_1im]Cl (◇), [C_4C_1im][TOS] (◇), [C_4C_1im][SCN] (◆), or [C_4C_1im][DCA] (◆), at 303.2 K. Data measured in this work or taken from the literature.[15]

interactions and facilitate its transfer into the vicinity of the cluster. This suggests a relationship between the efficiency of the counterion in hydrotropy and its hydration energy, which will be explored below.

In order to quantify the efficiency of the hydrotropes studied, the Setschenow constants of naproxen and ibuprofen in their aqueous solutions were calculated in this work (section S3 of the SI) and are reported in Table S12. To quantify the hydration energy of the counterions or, in other words, the strength of their interaction with water, their Gibbs solvation energy in water was estimated using the model COSMO-RS, as explained in section S4 of the SI. Finally, the Setschenow constants were correlated against the Gibbs solvation energy of the counterions of the hydrotropes. These results are depicted in Figure 3.

Figure 3 reveals excellent correlations between the Setschenow constants of naproxen and ibuprofen in aqueous solutions of [C_4C1_1m]Cl, [[C_4C1_1m][TOS], [[C_4C1_1m][SCN], and [[C_4C1_1m][DCA], and the Gibbs solvation energy of the corresponding counterions chloride, [TOS], [SCN], and [DCA]. This extraordinary result confirms the importance of using counterions with low hydration energies, paving the way for developing new hydrotropes with higher efficiency, and establishes an elegant connection between the stabilization of micelles due to the use of counterions that do not easily hydrate and the stabilization of apolar aggregates in hydrotropy.

To conclude, it was here shown that the classical choice of ionic hydrotropes based on small, densely charged ions such as

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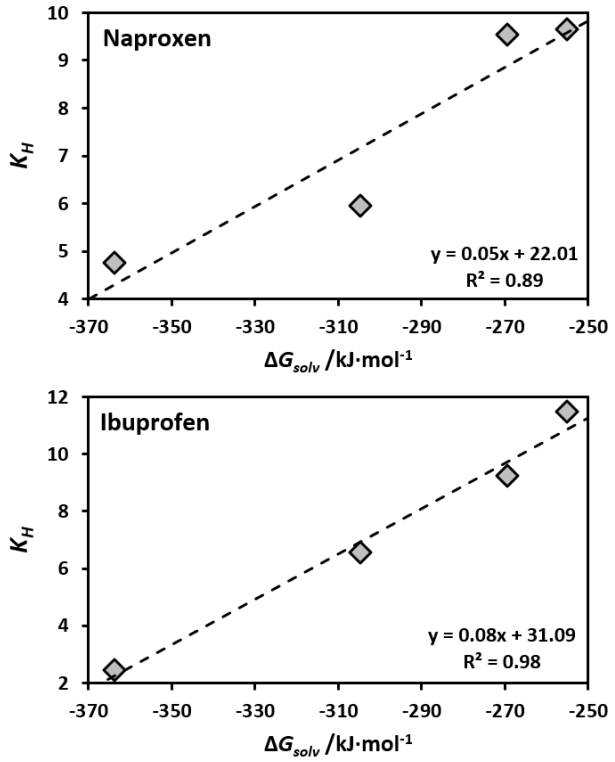

Figure 3. Setschenow constants of naproxen (top) and ibuprofen (bottom) in aqueous solutions of the ionic hydrotropes [C_4C_1im]Cl, [C_4C_1im][TOS], [C_4C_1im][SCN], or [C_4C_1im][DCA], as a function of the Gibbs hydration energy of the counterion estimated using COSMO.RS. The dashed lines are the straight line obtained using the method of least squares.

sodium or chloride is unfounded and does not lead to the best possible ion combination. In fact, due to the necessity of both ions to aggregate around the solute, either due to the hydrophobic effect or the minimization of local charge, hydrotropes comprised of amphiphilic ions are superior to hydrotropes with a highly hydrophilic counterion. A schematic illustration of this phenomenon is depicted in Figure S10. Furthermore, the impact of the counterion in the solubility enhancement of hydrophobic solutes follows the Hofmeister series for highly hydrophobic solutes. This is a very important result, since it not only sheds light on the mechanism of hydrotropy with ionic hydrotropes and the role of their counterions, it also reveals the Hofmeister series as a guide to design new and more efficient ionic hydrotropes. These conclusions based on anionic counterions are expected to hold also for cationic counterions. This is particularly useful considering the extensive literature available on the Hofmeister series of cation and anions that may serve as a basis to choose the best possible cation/anion combination to form the most efficient hydrotrope. Finally, the results discussed in this work reveal that ionic liquids, for some reason rarely explored in the field of hydrotropy, may be the most efficient ionic hydrotropes.

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Conflicts of interest

There are no conflicts to declare.

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