Glycerol Ethers as hydrotropes and their use to enhance the solubility in water of phenolic acids

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ABSTRACT:

The use of glycerol ethers (with alkyl side chains ranging from one to six methyl groups) as hydrotropes to enhance the solubility of gallic and syringic acids in water was here studied. These compounds were selected due to their biological and industrial applications and for serving as model molecules for lignin solubilization. The results obtained were compared against traditional cosolvents, demonstrating the exceptional hydrotropic ability of glycerol ethers. Setschenow constants show that the hydrophobicities of both solute and hydrotrope play an important role in the solubility enhancement by hydrotropy, shedding light into its molecular mechanism. The solubility curves of gallic acid and syringic acid in the aqueous glycerol ether solutions were fitted using a recently proposed statistical thermodynamics-based model. This allowed the estimation of solute recovery from hydrotropic solution by using water as the antisolvent. Unlike what is usually claimed it is here shown that in some conditions it is impossible to recover the solute by simply adding water. This analysis paves the way for a rational design and selection of hydrotropes, in which both solubility enhancement and solute recovery are critical parameters to be taken into account.

INTRODUCTION:

The concept of sustainable chemistry acquired great importance in the design of chemicals and processes less aggressive to the environment. Aiming at designing more sustainable

extraction processes, the combination of alternative solvents from renewable and biological sources is an important cornerstone of Green Chemistry,[1,2] combined preferentially with water, the greener universal solvent.[3–5] However, the low solubility in water of many organic compounds, some of which present relevant bioactivity, is one of the main shortcomings regarding the use of water to extract valuable compounds.[6] Increasing the solubility of poorly soluble substances in aqueous media, typically achievable by the addition of a cosolvent, plays an important role in the purification of bioactive compounds as well as in their formulation and bioavailability studies.[7,8]

Hydrotropes are a class of water-soluble compounds with an amphiphilic structure that are able to increase the solubility of hydrophobic substances in water.[9] Hydrotropy has been applied in several scientific fields, such as lignin and cellulose dissolution and fractionation, with great success.[10–15] Hydro- tropes can extend the applicability of water as a solvent to water-insoluble compounds, thus being highly relevant to Green Chemistry. However, since proposed by Neuberg[16] in 1916, most compounds studied as hydrotropes are petrochem- ical-based, such as sodium benzenesulfonate (SBS), sodium toluene sulfonate (STS), or sodium xylene sulfonate (SXS).

Nonionic alkyl-hydrotropes such as ethylene glycol ethers and propylene glycol ethers have also been proposed.[9,17,18] Recently, glycerol ethers have been shown to behave as hydrotropes, making them a promising biobased alternative for the commonly petrochemical-based hydrotropes,[19] while possessing lower vapor pressures and higher boiling points than their glycol ether counterparts.[20]

Glycerol ethers are amphiphilic compounds that possess a central hydrophilic glycerol backbone, conferring them a certain degree of polarity, and apolar alkyl side chains.[19–21] Besides glycerol being abundantly available (as a byproduct of biodiesel production, for example[22]), glycerol ethers are synthesized from it via a green pathway.[23] Moreover, glycerol ethers may be viewed as designer molecules, since it is possible to tune their physicochemical properties by changing the number and size of their alkyl groups.[19,21,24–26] The name of these compounds is usually abbreviated as [*x*.*y*.*z*], where *x*, *y*, and *z*, as shown in *Figure 1*, represent the number of carbon atoms of the alkyl chains linked to the oxygens in the three different positions of the glycerol backbone. A value of zero in any of these variables means that there is

a proton linked to the oxygen instead of an alkyl chain; i.e., there is a hydroxyl group in that position.

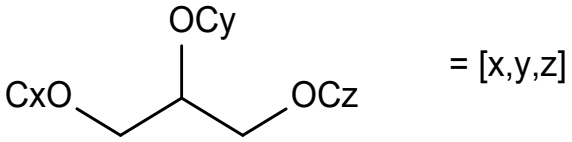

Figure 1. *Nomenclature for the alkyl glycerol ethers studied in this work.*

So far only a few works have been reported regarding the use of monoglycerol ethers as hydrotropes. Moity et al.[27] prepared three pentyl and three aryl 1-*O*-monoglyceryl ethers via esterification from glycerol, all presenting low volatility (vapor pressure below 0.01 kPa), and investigated their potential as hydrotropes. The results obtained show great solubility enhancement of a hydrophobic dye (Disperse Red 13), especially when using aryl monoglycerol ethers. Lebeuf et al.[28] have also studied the hydrotropic potential of mono-, di-, and trialkyl glycerol ethers for a hydrophobic dye (Disperse Red 13). Some of the compounds studied, such as [2.1.1], [3.1.1], [4.1.1], and [2.2.2], have a solubility limit, not being fully miscible with water, and are also the most volatile. Among the hydrotropes studied, [5.0.0] presents the greater solubilization power at low concentrations (up to 30 wt %) and possesses the highest boiling point (262 °C), making it one of the best candidates to be used as a hydrotrope in that case.

The present work investigates the effect of the alkyl sidechain of glycerol ethers on the solubility enhancement of two phenolic acids, the poorly water-soluble gallic and syringic acids. They were selected as model compounds for this study due to their relevant bioactivities such as strong antioxidant properties,[29,30] their presence in a wide variety of natural organic matrices and industrial applications,[30,31] and their different levels of polarity, with syringic acid being more hydrophobic than gallic acid (suggested by their different octanol/water partition coefficients[32]). Moreover, gallic and syringic acids are monomers of lignin and excellent model molecules for its solubility in hydrotropic systems, an active area of research.[11−13,33] The experimental data obtained was used to better understand the mechanism of hydrotropy, through the calculation of Setschenow constants.[34] Addition- ally, a recently proposed thermodynamics model of coopera- tive hydrotropy, developed by Shimizu and Matubayasi,[35] was used to fit the solubility data, enabling an analysis for the estimation of the

recovery ease of the solutes from the hydrotropic systems by using water as the antisolvent.

EXPERIMENTAL SECTION:

Chemicals. The chemicals used in this work are displayed in *Table 1*, along with their sources and mass purities. Water was double distilled, passed across a reverse osmosis system, and further treated with a Milli-Q plus 185 water purification apparatus. The alcohols were dried and distilled over calcium hydride previous to being used.

Table 1. *List of Substances Used in This Work along with Their CAS Number, Source, and Purity*

substance	CAS number	source	purity (wt %)
glycidol	556-52-5	Sigma-Aldrich	96
epichlorohydrin	106-89-8	Sigma-Aldrich	99
methanol	67-56-1	Scharlab	>99
ethanol	64-17-5	Scharlab	>99
sodium hydroxide	1310-73-2	Scharlab	98
hydrochloric acid (37%)	7647-01-0	Fisher	
propan-1-ol	71-23-8	Alfa Aesar	99.5
butan-1-ol	71-36-3	Alfa Aesar	>99
pentan-1-ol	71-41-0	Alfa Aesar	>99
hexan-1-ol	111-27-3	Alfa Aesar	>99
calcium hydride	7789-78-8	Acros Organics	>93.0
gallic acid	149-91-7	Merck	>99.5
syringic acid	530-57-4	Acros Organics	>98.0
glycerol	56-81-5	Fisher Chemical	>99.8
[1.0.0]	623-39-2	this work	>98[b]
[2.0.0]	1874-62-0	this work	>99[b]
[3.0.0]	61940-71-4	this work	>99[b]
[4.0.0]	624-52-2	this work	>99[b]

[5.0.0]	22636-32-4	this work	>99[b]
[6.0.0]	*a*	this work	>99[b]
[1.0.1]	623-69-8	this work	>99[b]
[2.0.2]	4043-59-8	this work	>99[b]

Synthesis of Glycerol Ethers. A scale up to 3 mol of the previously described glycerol ether synthesis was carried out.[24,25] Thus, in order to synthesize glycerol monoethers, 45 mol of alcohol and sodium hydroxide (20 mol % with respect to glycidol) was placed into a round bottomed flask. The reaction mixture was stirred and heated at 338 K, under argon, until total dissolution of the catalyst (NaOH). Then, glycidol (3 mmol) was added dropwise. The reaction was monitored at different times by extracting samples that were neutralized with 0.3 M HCl previous to injection in a Hewlett- Packard 7890 series II GC (Gas Chromatography), as described in section S1 of the *Supporting Information*. After the total consumption of glycidol, the reaction was quenched with 0.3 M HCl, and the salt formed (sodium chloride) was filtered off. Finally, the excess of the starting alcohol was eliminated by reduced pressure distillation, and glycerol monoethers were purified by vacuum distillation.

To synthesize symmetric glycerol diethers, 45 mol of the corresponding alcohol and the catalyst NaOH (4.2 mol) was placed into a round bottomed flask. The mixture was stirred and heated at 338 K under argon until total dissolution of the base. Then, epichlorohydrin (3 mmol) was added dropwise. Reactions were monitored by GC until total consumption of epichlorohydrin. Then, the reaction was also quenched with HCl 0.3 M and salts were filtered off. Finally, the excess of the starting alcohol was distilled and recovered, and the resulting glycerol diether was purified by vacuum distillation.

The purity of the products was checked by proton and carbon nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR), recording the spectra in a Bruker Avance 400 MHz device, and using DMSO-d_6 (dimethyl sulfoxide-d_6) as solvent (with chemical shifts δ in ppm). All the obtained spectra and the water content of each product (measured using Karl Fischer titration) can be found in Section S1 of the *Supporting Information*.

Solubility Measurements. The solubility of the phenolic acids (gallic acid or syringic acid) was measured by the analytical isothermal shake-flask method, previously described in detail.[6] The phenolic acid was added in excess to each hydrotrope aqueous solution. For the aqueous systems the samples were equilibrated in an air oven at (303.2 ± 0.5) K under constant stirring (950 rpm) and an equilibration time of 72 h, using an Eppendorf Thermomixer Comfort equipment. For the pure glycerol ethers, which are more viscous than their aqueous solutions, the samples were placed over plate stirrers inside a thermostatic water bath at (303.2 ± 0.1) K for 72 h. The equilibration conditions were previously optimized.[36,37]

After equilibrium was reached (72 h), all samples were centrifuged at (303.2 ± 0.5) K for 20 min using a Hettich Mikro 120 centrifuge operating at 4500 rpm, in order to separate the excess undissolved solute from the liquid phase. After centrifugation, all samples were placed in an air bath equipped with a Pt 100 probe and a PID controller at the temperature used in equilibrium assays during 2 h. Then, the samples of the liquid phase were carefully collected and diluted in ultrapure water, and the amount of phenolic acid was quantified by UV spectroscopy using a SHIMADZU UV-1700, Pharma-Spec spectrometer at 262 and 267 nm for gallic and syringic acid, respectively. At least three individual samples were quantified for each system.

RESULTS AND DISCUSSION:

Solubility Curves. The solubility of gallic acid and syringic acid (see Figure S9 for chemical structures) in aqueous solutions of glycerol ethers was measured in the entire concentration range, at 303.2 K, and is reported in Section S2 of the *Supporting Information* (Tables S2−18). Since [6.0.0] forms a two-phase system with water[19] at concen- trations below 38 wt % its hydrotropic capability was studied only for gallic acid in the single-phase region.

The solubility data for gallic acid is shown in *Figure 2*, where S and S_0 represent the solubility (mol/L) of gallic acid in the aqueous solutions of the hydrotrope and in pure water, respectively. Choosing attainable maximum solubility as the metric of interest, the ability of the linear glycerol ethers to enhance the solubility of gallic acid increases in the following order

[6.0.0] < [5.0.0] < [4.0.0] < [3.0.0] < [2.0.0] < [1.0.0]. Moreover, [1.0.1] is better than [2.0.2] while glycerol shows the least solubility enhancement.

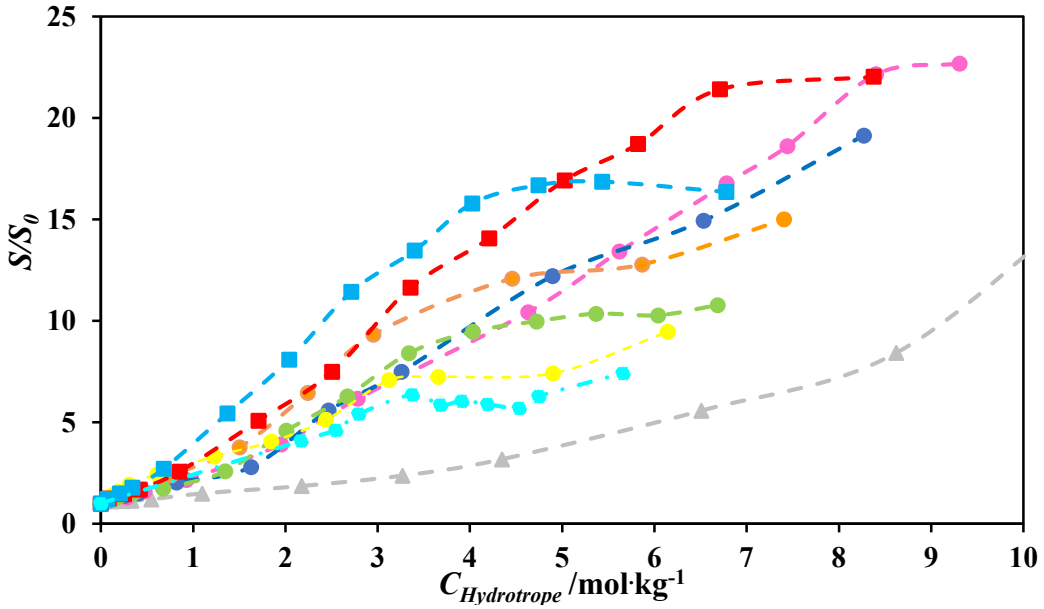

Figure 2 *Effect of glycerol ether (hydrotrope) concentration on the solubility of gallic acid in aqueous solutions of [1.0.0] (pink ●), [2.0.0] (blue ●), [3.0.0] (orange ●), [4.0.0] (green ●), [5.0.0] (yellow ●), [6.0.0] (aqua ●), [1.0.1] (red ■), [2.0.2] (blue ■), and glycerol (gray ▲), at 303.2 K. S/S0 is the relative solubility (expressed in mol/L) of the solute, and CHydrotrope is the concentration of the hydrotrope in the solvent (solute-free basis). Dashed lines are visual guides.*

This initial analysis suggests that the shorter the alkyl chain of the hydrotrope, the better the solubility enhancement. Note that the maximum solubility of gallic acid in aqueous [1.0.0] or [1.0.1] is about the same, with the plateau being reached at a lower concentration for the [1.0.1] curve.

The solubility data for syringic acid is depicted in Figure 3. Contrary to what is seen in Figure 2, most of the solubility curves depicted in Figure 3 pass through a maximum, with glycerol and [1.0.0] as the exceptions, suggesting an optimal concentration of the hydrotrope. Again considering attainable maximum solubility as the metric of interest, the conclusions drawn from Figure 2 for gallic acid hold true for syringic acid as well. Hence, it appears that the smaller the hydrotrope the better the solubility enhancement. Interestingly, the increase in solubility of syringic acid is proportionally much more pronounced than that for gallic acid.

For instance, it is possible to reach a 77-fold increase in the solubility of syringic acid using [1.0.1] while a 22-fold increase in solubility was achieved for gallic acid with the same hydrotrope.

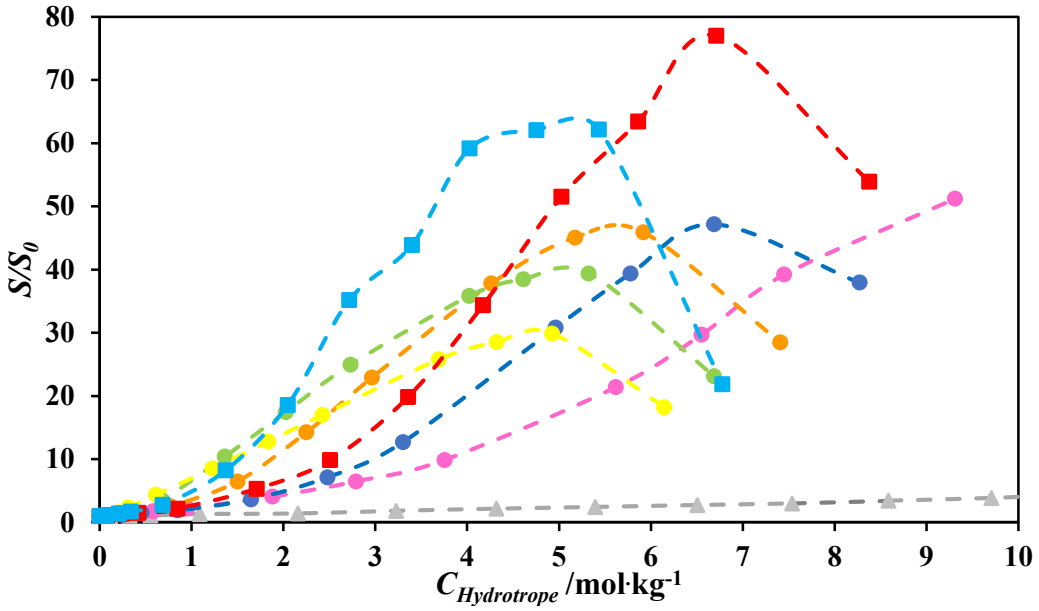

Figure 3. *Effect of glycerol ether (hydrotrope) concentration on the solubility of syringic acid in aqueous solutions of [1.0.0] (pink ●), [2.0.0] (blue ●), [3.0.0] (orange ●), [4.0.0] (green ●), [5.0.0] (yellow ●), [1.0.1] (red ■), [2.0.2] (blue ■), and glycerol (gray ▲), at 303.2 K. S/S0 is the relative solubility (expressed in mol/L) of the solute, and CHydrotrope is the concentration of the hydrotrope in the solvent (solute-free basis). Dashed lines are visual guides.*

The solubility enhancement of gallic and syringic acids obtained using glycerol ethers as hydrotropes was compared against results using cosolvency with traditional solvents (*Figure 4*). As *Figure 4* clearly demonstrates, glycerol ethers are much better solubilizing agents for gallic acid than traditional cosolvents such as methanol, acetonitrile, and propan-2-ol. Even glycerol, the worst hydrotrope studied in this work, is better than traditional cosolvents. While methanol provides higher solubility values than glycerol in the solubilization of syringic acid, it is much inferior to [1.0.1] in most of the concentration range. Methanol is, indeed, commonly added to enhance the solubility of hydrophobic substances but possesses high volatility and toxicity,[38] contrary to the glycerol ethers studied in this work.[24,25,39,40] It is interesting to note that the methanol solubility curve for gallic acid presents a linear shape, in contrast with its sigmoidal shape for syringic acid,

similar to what is expected in hydrotropy.

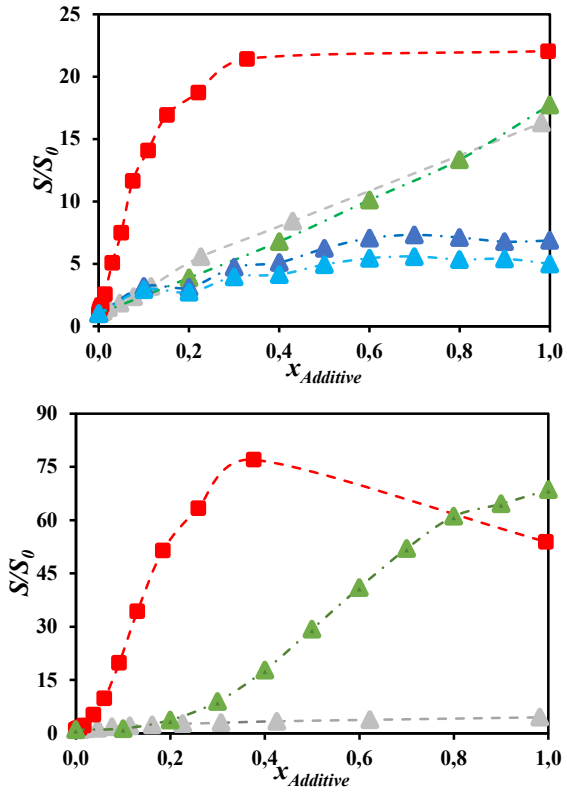

Figure 4. *Solubility enhancement of gallic acid (left panel) and syringic acid (right panel) using the hydrotropes [1.0.1] (red ■), and [0.0.0] (gray ▲, this work) and the cosolvents methanol (green ▲),41,42 ethanol (yellow ▲),43 acetonitrile (dark blue ▲),44 and propan-2-ol (light blue ▲).44 S/S0 is the relative solubility (expressed in mol/L) of the solute, and the x-axis represents the mole fraction of the additive (hydrotrope or cosolvent) in the solvent (solute-free basis). Dashed lines are visual guides.*

Dilute Hydrotrope Region. The pronounced effect of glycerol ethers as hydrotrope agents, when compared to traditional organic solvents, is of great interest for extraction processes, especially in the replacement of traditional volatile organic compounds. However, apart from studying the entire concentration range of the hydrotrope, the careful analysis of the dilute hydrotrope region is also important for the following reasons. First, from an application-wise perspective, using smaller quantities of additives (hydrotropes) is economically preferable. Second, from a fundamental perspective the identification of the molecular mechanism of hydrotropy is easier in the dilute region where effects can be isolated (contribution from

the hydrotrope self-association in the bulk phase can, for instance, be neglected). To study the dilute region the Setschenow constant was used.[34] Originally this was proposed as an empirical approach to describe the effect of a salt or cosolvent on the solubility of a compound in aqueous solution and has since been applied to describe the effect of hydrotropes on the aqueous solubility of solutes.[36,37] It has been shown, using statistical thermodynamics, that this approach has a sound physical basis in the dilute region.[45]

The Setschenow constant[34] quantifies the change in the solubility of a solute due to the presence of a hydrotrope, in the dilute region. It is herein defined as

$$\ln(S_s) = K_H \cdot C_H \qquad (1)$$

where S_s is the molar solubility of the solute, K_H is the Setschenow constant, and C_H is the molarity of the hydrotrope. Equation 1 is valid from a hydrotrope molarity of zero up to a value where the variation of the natural logarithm of the solubility of the solute remains linear with the increase in the molarity of the hydrotrope (about 5 wt % for the hydrotropes studied in this work).

Besides being useful to quantify the hydrotropic power of a substance (albeit in the dilute region), Setschenow constants can also be linked to statistical thermodynamics. The Setschenow constants calculated as per eq 1 are related to Kirkwood−Buff integrals (KBI) through the following expression:[45]

$$K_H = G_{S,H} - G_{S,W} \qquad (2)$$

where $G_{S,H}$ is the KBI between solute and hydrotrope and $G_{S,W}$ is the KBI between solute and water. *Equation 2* shows that the higher the Setschenow constant is, the higher the preference of the solute to interact with the hydrotrope instead of with water and, consequently, the higher the solubility enhancement of the solute.

The Setschenow constants were calculated (assuming density of the systems in the dilute region equal to that of water) for all solute−hydrotrope pairs reported in this work, except for [6.0.0] since solubility data in the dilute region is not available for this compound. These results are reported in *Table 2*. Interestingly, the values obtained are in contradiction with the

initial qualitative analysis from *Figures 2* and *3*. That is, the hydrotropic power of glycerol ethers in the dilute region increases with the increase in size of the alkyl side chain, in line with previous studies:[28] [0.0.0] < [1.0.0] < [2.0.0] < [3.0.0] <[4.0.0] < [5.0.0].

The results reported in Table 2 are in agreement with a previous study by Bauduin and co-workers[17] that suggested the apolar volume of a hydrotrope to be directly connected with its capability to enhance the solubility of a solute. In fact, the progressive increase, through the addition of methyl groups, in apolar volume of the glycerol ethers seems to positively correlate with the Setschenow constants obtained, shedding light into the molecular mechanisms of hydrotropy.

Considering *eq 2*, which has shown that Setschenow constants increase if the KBI of the solute−hydrotrope pair increases or the KBI of the solute−water pair decreases, it makes sense that apolarity or hydrophobicity plays a role in hydrotropy. An increase in the hydrophobicity of the solute should lead to a decrease of its interaction with water, leading to a decrease of the solute−water KBI and a consequent increase in the Setschenow constant. This is exactly what is seen in this work: for the same hydrotrope, the Setschenow constant obtained for systems containing syringic acid are higher than that of gallic acid (syringic acid has a higher octanol/water partition coefficient than gallic acid, suggesting it is more hydrophobic than gallic acid[32]). On the other hand, increasing the hydrophobicity of the hydrotrope weakens its interaction with water, promoting interaction with the hydrophobic solute, leading to an increase in the solute− hydrotrope KBI, increasing the Setschenow constant, in accordance to what is reported in *Table 2*.

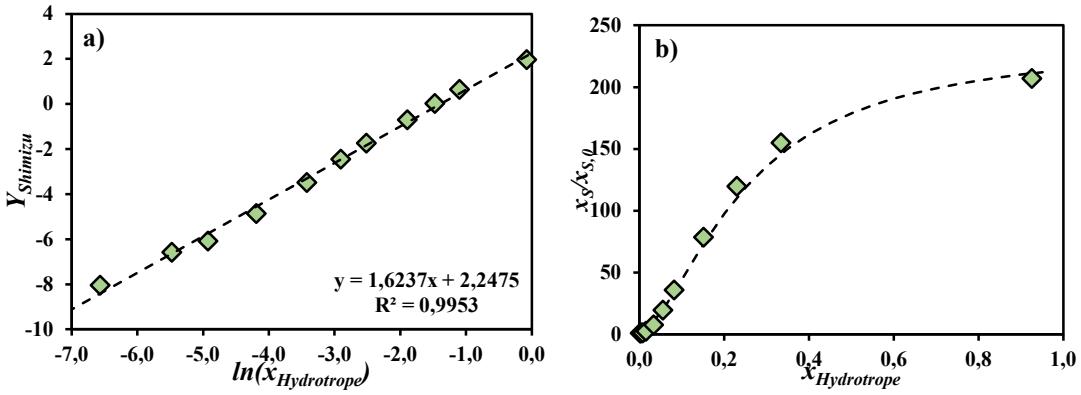

Figure 5. *Linearized plot of the cooperative hydrotropy model based on eq 4 (left panel: green ◆,*

experimental data; dashed line, least-squares fit) and fitted experimental data (right panel: green ◆, experimental data; dashed line, cooperative hydrotropy model) for the water−[3.0.0]−syringic acid system. The x-axis represents the mole fraction of the hydrotrope in the ternary system (as opposed to its mole fraction in the solvent free of solute).

It is not yet clear why there is an inversion on the behavior of the hydrotropic power of glycerol ethers above a certain concentration range, with more hydrophobic hydrotropes being better at low concentrations and more hydrophilic hydrotropes being better at higher concentrations. The Setschenow analysis above reveals that the size of the alkyl chain length appears to be the dominating factor at low concentrations. However, it is expected that increasing the hydrotrope concentration will also increase the activity coefficient of water, as supported by the immiscibility observed for [6.0.0]. That is, increasing the alkyl chain length of the hydrotrope increases its hydrophobicity, leading to a less favorable interaction to water for high hydrotrope concentration. Thus, above a certain concentration of these hydrotropes, the nefarious effect of being too hydrophobic prevails over favorable solute−hydrotrope interactions, leading to a drastic negative impact in the hydrotropic behavior.

Modeling. The solubility data obtained in this work was fitted using a statistical thermodynamics-based model developed by Shimizu and Matubayasi.[35] This model based on the cooperativity concept was developed not only to describe the usual sigmoidal solubility curves found in hydrotropy but also to give insight into the interactions between solute and hydrotrope molecules. The model can be expressed as

$$ln\left[\frac{1-\frac{x_S}{x_{S,0}}}{\frac{x_S}{x_{S,0}}-\left(\frac{x_S}{x_{S,0}}\right)_{max}}\right] = m \cdot ln(x_H) + b \qquad (3)$$

where x_S is the solute saturation mole fraction (solubility) in the hydrotropic system, $x_{S,0}$ is the solute saturation mole fraction in water, and x_H is the mole fraction of the hydrotrope. Note that x_H is not the mole fraction of the hydrotrope in a solute-free basis but its mole fraction in the ternary water− hydrotrope−solute system; interconversion between them is done assuming the density of the mixture equal to that of water. From the definition of x_S and $x_{S,0}$ it becomes clear that the term $x_S/x_{S,0}$ represents the relative solubility in the mole

fraction basis. As such, $(x_S/x_{S,0})_{max}$ (henceforth *max*) is the maximum of the relative solubility caused by a given hydrotrope, i.e., the value of the plateau in the sigmoidal solubility curve. Finally, m and b are parameters that give insight into the molecular interactions between solute and hydrotrope. More specifically, m represents the number of hydrotrope molecules in the vicinity of the solute.[35]

Due to the difficulty of identifying a clear solubility plateau in the many of the systems studied in this work, the parameter max was treated as an adjustable parameter of the model. Note that *m* and *b* are not adjustable parameters of the model, since they are directly calculated from the experimental data and the max parameter. The modeling algorithm used goes as follows. A value is arbitrarily chosen for variable max. Then, the *m* and *b* parameters are extracted from the experimental data as the slope and intercept of the linearized curve defined as:

$$Y = ln\left[\frac{1-\frac{x_S}{x_{S,0}}}{\frac{x_S}{x_{S,0}}-\left(\frac{x_S}{x_{S,0}}\right)_{max}}\right]; x = ln(x_H) \quad (4)$$

Using the calculated m and b parameters, the experimental data is reproduced using the model and the quadratic error between the predicted and the experimental data is calculated. Variable max is then varied until the sum of the quadratic errors is minimized. This procedure for the application of the model is illustrated in *Figure 5a* with *eq 4* and *Figure 5b* with the actual fitting, both for the syringic acid−[3.0.0] solute hydrotrope pair. Fitted curves for all systems herein studied are depicted in Section S3 of the Supporting Information (*Figures S10 and S11*).

As *Figures S10* and *S11* show (see Section S3 of the Supporting Information), the model reproduces the experimental data quite well. It is curious to note that the characteristic sigmoidal shape of the hydrotropic solubility curves is much more patent in the systems with syringic acid than in the systems with gallic acid. Moreover, it is important to note that expressing the composition of the hydrotrope in the actual ternary system instead of its composition in the solvent (solute-free basis) removes the maxima seen in the solubility

curves depicted in *Figures 2* and *3*. No clear pattern can be identified on the model parameters, which are reported in *Table S19* of the Supporting Information.

The cooperative model employed in this work (eq 3) can be applicable not only to cooperative (sigmoidal) solubility increases but also linear (noncooperative cases), such as those seen for gallic acid. In the latter case, m becomes close to 1, leading to a very large max variable. Thus, the general applicability of the model is supported by its success in describing both linear and sigmoidal solubility curves.

Solute Recovery. Besides quantifying their dissolution ability, it is fundamental to address the recovery of solute from hydrotropic solutions. For most organic solvents, a simple evaporation suffices. However, evaporating water from a hydrotropic solution would increase hydrotrope concentration which, generally, would increase the solubility of the solute. Moreover, the hydrotropes are often non- or poorly volatile.

There is, however, a clever turnaround that allows for the easy recovery of solute from a hydrotrope solution with similar energy cost when compared to traditional solvents: the use of water as the antisolvent. As proposed in previous works,[18,46–48] addition of water to a hydrotropic solution may induce the precipitation of the solute due to the dilution of the hydrotrope, providing an easy and straightforward approach to recover the solute in high purity.

Whether this approach to solute recovery is feasible was here evaluated by calculating the recoverable fraction of dissolved solute, using the solubility curves modeling reported in the previous section. The calculation algorithm and detailed results are reported in Section S4 of the Supporting Information.

Figure 6 illustrates the recovery curves (recovered solute fraction versus water volume fraction added) obtained using the hydrotrope [1.0.1] for gallic acid and syringic acid. Note that a negative solute fraction is possible, meaning that there is no precipitation and the system is no longer saturated, thus, being able to dissolve more solute.

Surprisingly, addition of water does not always lead to solute precipitation. Considering the examples depicted in Figure 6, both the hydrotrope and its composition clearly play a role in

determining the feasibility of recovering the solute by using water as the antisolvent. For instance, in this case (the gallic acid−[1.0.1] system), the solute can only be recovered if the hydrotrope mole fraction is in the 0.05−0.4 range, with a maximum recovery of 17% achieved in the 0.2−0.4 hydrotrope mole fraction range. If the hydrotrope mole fraction is higher than 0.4, the solute may still be recoverable but only after the addition of a large quantity of water. Below a mole fraction of 0.05, solute recovery is unfeasible. These conclusions are similar for the syringic acid−[1.0.1] system. In this case, the solute can be recovered in a narrower mole fraction window, but up to 70% can be recovered. Despite the increased volume of water when water is added to a hydrotropic system, the hydrotrope becomes less concentrated, which makes hydrotropy less effective. Whether any amount of solute precipitates from a hydrotrope solution after adding water is determined by the trade-off between these two factors. Thus, the recovery of solute is more favorable as the slope of the solute solubility curve increases, which corresponds to a bigger change in solubility due to a smaller change in hydrotrope concentration. It is also important to note that since syringic acid is much less soluble in water than gallic acid, it is easier to recover it since the first factor (solute dissolution in the new water volume) loses importance.

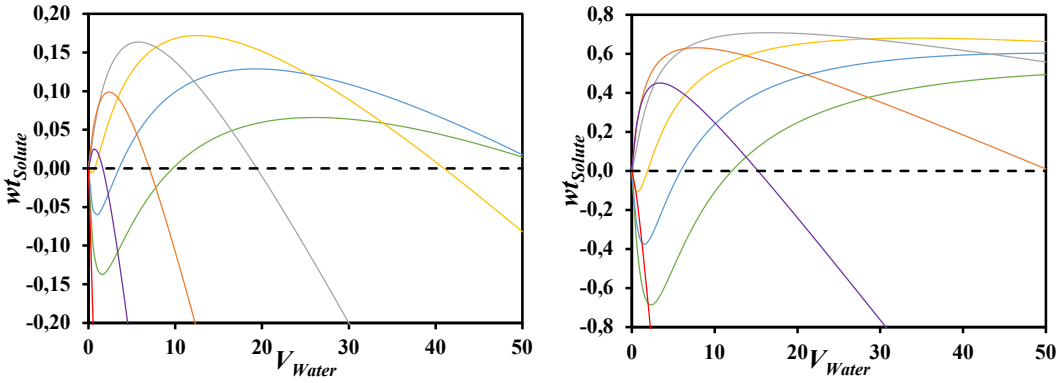

Figure 6. *Estimated fraction of gallic acid (left panel) and syringic acid (right panel) recovered from hydrotrope solution (wtSolute) by the addition of water (VWater is the volumetric ratio between added water and initial system), with initial hydrotrope ([1.0.0]) mole fractions of 0.01 (red line), 0.05 (purple line), 0.1 (orange line), 0.2 (gray line), 0.4 (yellow line), 0.6 (blue line), and 0.8 (green line). A negative value indicates that no precipitation happens, with the system being able to dissolve further solute.*

Moreover, the slope of the solubility curves tends to be higher in mid-composition ranges of the hydrotrope (sigmoidal shape), explaining the recovery windows positioned in midhydrotrope mole fractions. *Figure S12* reveals that, in terms of gallic acid recovery, it is better to use a hydrotrope mole fraction of 0.2−0.8 for the most hydrophilic hydrotropes ([1.0.0] and [2.0.0]), while a 0.05−0.2 window is better for the least hydrophilic ones.

Interestingly, it is impossible (using the addition of water) to recover gallic acid dissolved in aqueous [5.0.0] solutions. The same conclusions hold true for syringic acid, as *Figure S13* shows, albeit in narrower mole fraction windows, similarly to what was concluded through the analysis of *Figure 6*. The biggest difference is the fraction of solute recovered, which is much higher for syringic acid than for gallic acid, due to the almost 10-fold difference between their solubilities in pure water.

CONCLUSION

The solubilities of gallic acid and syringic acid were measured in aqueous solutions of glycerol ethers, a recently proposed new class of hydrotropes, demonstrating their excellent hydrotropic ability. Their solubilization capacities are more prominent for the smaller, more hydrophilic hydrotropes and are superior to those of traditional organic cosolvents.

The Setschenow constants for the hydrotropic systems shed light into the hydrotropy mechanism of these systems. The results show that the hydrophobicity of the hydrotrope plays a major role in hydrotropy, being dominant in the dilute region. Furthermore, the hydrophobicity of the solute is also important, since its relative solubility enhancement is directly linked to it.

The experimental data herein obtained was fitted using the cooperative hydrotropy model. It provided appropriate fitting and allowed for the analysis of the feasibility of recovering solute from hydrotropic solutions by the addition of water. It was herein shown that solute recovery is not always possible.

As such, the choice of hydrotrope and operating concentration for a given application should consider not only the solubility enhancement provided by the hydrotrope but also the ease of solute recovery from the system.

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