

This is a repository copy of *Geminal Diol of Dihydrolevoglucosenone as a Switchable Hydrotrope : A Continuum of Green Nanostructured Solvents*.

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/145772/>

Version: Accepted Version

Article:

De Bruyn, Mario orcid.org/0000-0002-9687-1606, Budarin, Vitaliy L., Misefari, Antonio et al. (8 more authors) (2019) Geminal Diol of Dihydrolevoglucosenone as a Switchable Hydrotrope : A Continuum of Green Nanostructured Solvents. ACS Sustainable Chemistry and Engineering. pp. 7878-7883. ISSN 2168-0485

<https://doi.org/10.1021/acssuschemeng.9b00470>

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

The Geminal Diol of Dihydrolevoglucosenone as a Switchable Hydrotrope: Dissolution by Nanostructuralization

Mario De bruyn,*^[a]^[b] Vitaliy L. Budarin,^[c] Antonio Misefari,^[c] Seishi Shimizu,^[d] Heather Fish,^[d] Martin Cockett,^[d] Andrew J. Hunt,^[e] Heike Hofstetter,^[f] Bert M. Weckhuysen,^[b] James H. Clark,^[c] Duncan J. Macquarrie,^[c]

- ^{a.} Department of chemical and biological engineering, University of Wisconsin-Madison, 1415 Engineering Drive, 53706 Wisconsin, USA; debruyn@wisc.edu
- ^{b.} Faculty of Science, Debye Institute for Nanomaterials Science, Utrecht University, Universiteitsweg 99, CG Utrecht 3584, The Netherlands
- ^{c.} Green Chemistry Centre of Excellence, Department of Chemistry, University of York, YO10 5DD, York, United Kingdom
- ^{d.} Department of Chemistry, University of York, YO10 5DD, York, United Kingdom
- ^{e.} Materials Chemistry Research Center, Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Khon Kaen University, Khon Kaen, 40002, Thailand
- ^{f.} Department of Chemistry, University of Wisconsin-Madison, 1101 University Ave, Madison, WI, 53706, USA

ABSTRACT: The addition of water to dihydrolevoglucosenone (Cyrene) creates a solvent mixture with highly unusual properties and the ability to specifically and efficiently solubilise a wide range of organic compounds notably aspirin, ibuprofen, salicylic acid, ferulic acid, caffeine and mandelic acid. The observed solubility enhancement (up to 100-fold) can only be explained by the existence of micro-environments mainly centered on Cyrene's geminal diol. Surprisingly the latter acts as a reversible hydrotrope and regulates the polarity of the created complex mixture. The possibility to tune the polarity of the solvent mixture through the addition of water, and the subsequent generation of variable amounts of Cyrene's geminal diol, creates a continuum of green solvents with controllable solubilization properties. The effective presence of microheterogenities in the Cyrene/water mixture was adequately proven by 1) FT-IR/DFT showing Cyrene dimerization 2) electrospray mass-spectrometry demonstrating the existence of dimers of Cyrene's geminal diol and 3) the variable presence of single or multiple tetramethylsilane (TMS) peaks in the ¹H NMR spectra of a range of Cyrene/water mixtures. The Cyrene-water solvent mixture is importantly not mutagenic, barely ecotoxic, bio-derived and endowed with tuneable hydrophilic/ hydrophobic properties.

KEYWORDS: *Solvents – Nanostructure - Hydrotrope – Bio-based – Switchable - Sustainable*

INTRODUCTION

The dissolution of chemical substances is a key technology in the chemical industry, with over 20 megatonnes of solvent consumed per year.¹⁻³ Presently, the use of many conventional solvents has come under increasing scrutiny, due to their strongly negative environmental impacts and often high toxicities.⁴ In this respect, the Registration, Evaluation, Authorisation & restriction of CHemicals regulation (REACH) is already beginning to lead to restrictions in the use of many common conventional solvents (e.g. nitrobenzene⁵, 1,2-dichloroethane⁵⁻⁶), which has, in turn, reinforced the search for novel solvents with more benign characteristics. Ideally, these are also bio-based; examples being methyltetrahydrofuran, glycerol, γ -valerolactone, ethylacetate, and dihydrolevoglucosenone (Cyrene).⁷⁻¹⁰ The last of these is of particular importance as it is a rare bio-based dipolar aprotic solvent displaying similar solvent-characteristics to N-methylpyrrolidone (NMP) and dimethylforma-

mid (DMF), but while both NMP and DMF are extremely versatile and important solvents they also display reproductive toxicity (reprotoxity).⁸ In contrast Zhang *et al.* have reported that Cyrene is not mutagenic and barely ecotoxic, showing an LD50 > 2000 mg L⁻¹.⁹ Very recently the Circa Group, as the sole manufacturer of Cyrene, has received REACH Annex VIII approval, allowing it to import and/or manufacture up to 100 tonnes/year of Cyrene in the European Union.¹¹

Solubilization and extraction of solutes often require the use of (multiple) solvent mixtures and/or solubilizers added to the principal solvent.³ Besides bio-based solvents, the use of aqueous solvent systems, switchable solvents, ionic liquids, deep eutectic solvents, CO₂ tuneable solvents, CO₂ expanded liquids and liquid polymers also often have solid green credentials.¹²⁻¹⁴ The most common solubilizers are surfactants and hydrotropes and these are most often amphiphilic compounds which can enhance the aqueous solubility of hydrophobic compounds markedly.¹⁵⁻¹⁸ On a molecular level surfactants tend to feature longer

C8-C20 alkyl chains while hydrotropes typically have shorter alkyl tails ($\leq C4$) and/or aromatic rings.¹⁹ Hydrotropes are generally solids but they can also be liquids in which case they are known as "chameleonic solvents" or "solvo-surfactants".¹⁵ Examples of "chameleonic solvents" are the short-chain ethers of mono/di/tri propylene glycols, which can aid dissolution of organic substances in water by a hydrotropic mechanism but also by forming monophasic micro-emulsions. However, as with NMP and DMF, glycol ethers have known or suspected toxicity including reprotoxicity.¹⁵ Only recently, the underlying, general principle of hydrotrope-based solubilization was shown to be the result of non-specific association of hydrotropes with solutes, which more than compensates the per-hydrotrope solubilization inefficiency due to hydrotrope self-association.²⁰ Also, the sudden onset of solubilization at critical hydrotrope concentrations, which is another characteristic signature of hydrotropy, has been linked to enhanced hydrotrope self-association around the solute.²¹

Here we show that the addition of water to Cyrene, one of the new generations of bio-based solvents, can significantly increase the solubility of a range of organic molecules, even for those with very low water solubility (Figure 1A, table 1S_A/B). Furthermore, it is also apparent that the points of maximal solubilisation are actually controlled by the nature of the substrate. Crucial to this behavior is the observation that Cyrene interacts chemically, and reversibly, with water, forming its geminal diol [(1S,5R)-6,8-dioxabicyclo[3.2.1]octan-4,4-diol] (Figure 1B). Consequently, marked amphiphilicity is created in the Cyrene-water solvent system. When taken together with the characteristic S-shape curve of the solubility profiles as viewed from the H₂O side, we infer that Cyrene's geminal diol is behaving as a hydrotrope. The occurrence of a controllable equilibrium between Cyrene, its geminal diol and H₂O is remarkable in that it imparts tunability of the properties of the Cyrene solvent. Indeed, while Cyrene has been classified as a dipolar aprotic solvent, the introduction of water and the consequent formation of Cyrene's geminal diol introduces significant additional polarity from two hydroxyl groups. These two additional proton donor groups augment the existing proton-acceptor capacity of Cyrene and consequently enhance its overall hydrogen bonding capacity.

RESULTS AND DISCUSSION

The composition of the ternary Cyrene/water/geminal diol mixture (hereafter abbreviated as TM-H₂O) has been investigated with ¹H and quantitative ¹³C NMR. Figure 1B (and Table 2S_A) show its composition as a function of the initial amount of Cyrene added to water (in wt%) and with both the molar amounts of geminal diol and excess H₂O (*i.e.* water that has not engaged in forming the geminal diol) normalized to 1 mol Cyrene. The composition of the ternary mixture can thus be adequately described as [Cyrene normalized moles geminal diol; Cyrene normalized moles H₂O] couples (see figure 1B). This data allows the investigation of the equilibrium of the Cyrene hydration reaction (table 2S_B). Two different models for the Cyrene – water interaction/reaction have been considered: (i) one that follows the intuitive reaction stoichiometry in which one molecule of Cyrene reacts with one water molecule yielding

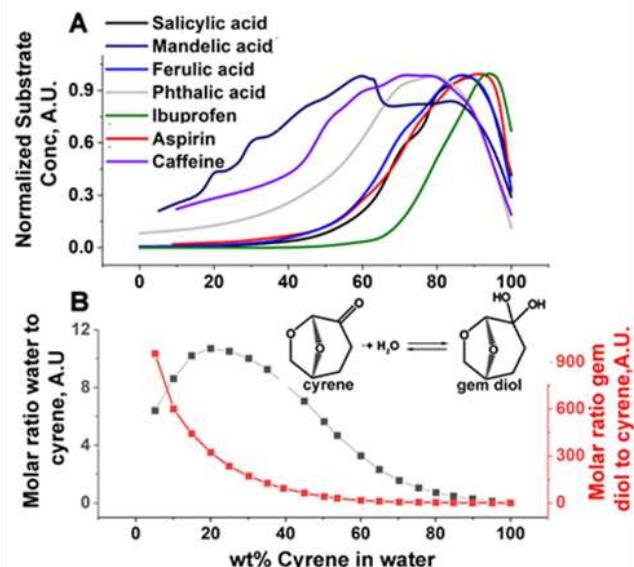


Figure 1. A) normalized solubility of a range of organic substrates B) the molar composition of the Cyrene-H₂O solution as a function of the initial Cyrene concentration (based on ¹H/¹³C NMR data).

the geminal diol (see Figure 2 A) and (ii) a reaction stoichiometry in which two water molecules are involved, one reacting with the Cyrene and one hydrogen bonding strongly to the geminal diol (Figure 2B). Model (i) is only valid at initial cyrene concentrations > 85 wt% from which point it displays a constant K_{eq}^1 (Figure 2A, yellow-striped zone). Alternatively, model (ii) (Figure 2B, cyan zone) yields a constant K_{eq}^2 up to < 50 wt% initial Cyrene concentration, suggesting that this model provides a more realistic description of the reaction within this concentration range. The zone between 50-85 wt% is not straightforwardly categorizable to either model and may therefore require consideration of the involvement of other species/complexes.

To obtain more insight in the structure of Cyrene-water solutions, a systematic FT-IR analysis of Cyrene and Cyrene-water solutions has been performed:

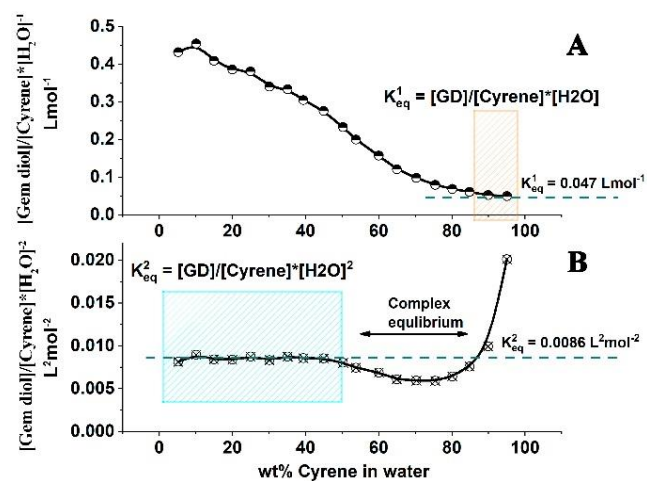


Figure 2. A) Linearization of the Cyrene-H₂O solution compositional data based on the natural Cyrene-geminal diol equilibrium involving one water molecule; B) Linearization of the Cyrene-H₂O solution compositional data based on the involvement of two water molecules in the equilibrium

Firstly, and most surprisingly, the FT-IR spectrum of pure Cyrene, with just a single carbonyl group, displays at least two different IR carbonyl absorption bands centered at about 1730 cm^{-1} (Figure 3A). Such an observation cannot relate to the opening of the acetal group because this only occurs in the presence of a strong acid and at temperatures $> 120\text{ }^{\circ}\text{C}$. The most plausible alternative explanation is that the carbonyl group sits in two or more different chemical environments. A Clausius Clapeyron plot obtained from the variation of the vapor pressure with temperature determined the ΔH_{vap} of Cyrene at 67 kJ mol^{-1} . This value divided by Cyrene's boiling point (476 K) gives a value for ΔS_{vap} of $140\text{ J mol}^{-1}\text{ K}^{-1}$. This is substantially higher than that predicted by Trouton's rule which states that the entropy of vaporization for many (but not all) liquids is about the same at $85\text{--}88\text{ J mol}^{-1}\text{ K}^{-1}$.²² Exceptions to this rule are the entropies of vaporization of water, ethanol, and formic acid, all of which form strong hydrogen bonding interactions in the liquid phase. A reasonable conclusion therefore is that the positive deviation from Trouton's rule for Cyrene is due to the existence of strong hydrogen-bonding interactions between Cyrene monomers. Consistent with this conclusion is the observation that the experimental FT-IR spectrum of Cyrene in excess CCl_4 , in which formation of higher order clusters of Cyrene molecules is likely to be impeded, reveals just a single carbonyl band (see Figure 3A).

In order to support this hypothesis, a series of density functional theory (DFT) calculations were carried out at the M062X/cc-pVDZ level on the Cyrene system. Geometry optimizations and vibrational frequency analysis allowed the simulation of IR spectra for each structure. As expected, the resulting simulated IR spectrum of the Cyrene monomer revealed just one single carbonyl stretching band (see SI). However, IR simulations of a number of different structural isomers of the Cyrene dimer revealed doublet carbonyl stretching bands where the structures of those dimers resulted in different chemical environments for the two carbonyl groups (see Figure 3B and the SI). Similarly, a simulated IR spectrum for one conformer of the Cyrene trimer revealed a triplet of carbonyl stretching bands (see SI).

Addition of water to Cyrene shows a progressive change in the relative intensities of the two carbonyl IR stretching bands, becoming equal at $\sim 24\text{ wt}\%$ water. This suggests a persistent presence of the Cyrene dimer over a large range of concentrations (Figure 4A/B). Likewise, the symmetric and asymmetric geminal diol OH stretches at 1080 and 1063 cm^{-1} also show a progressive variation in relative intensities with increasing water content (Figure 4C/D). Of particular note, in the $25\text{--}65\text{ wt}\%$ water range, rapid changes in the C-C skeletal vibrational bands of Cyrene at 906 and 917 cm^{-1} are observed which suggests involvement of the acetal oxygens (1020 and 984 cm^{-1} bands) in hydrogen bonding to *other Cyrene molecules, or to Cyrene's geminal diol or indeed with H_2O* (Figure 4C/D) (Figure 4C/D).²³

To gain further insight we evaluated the solubility profiles for a range of organic substrates (Figure 5 and Table 1S A/B), through linear regression, as a function of the 4 main components [Cyrene (Cy), Cyrene dimer, geminal diol (GD) & H_2O] and 4 possible molecular complexes 'Cyrene-geminal diol', 'geminal diol-water', 'geminal diol dimer' and 'Cyrene-water' (see Equation 1, Table 1 and Figure 5). These complexes then refer to the potential presence of micro-heterogeneities in the Cyrene- H_2O solvent mixture. As can be seen from Figure 5

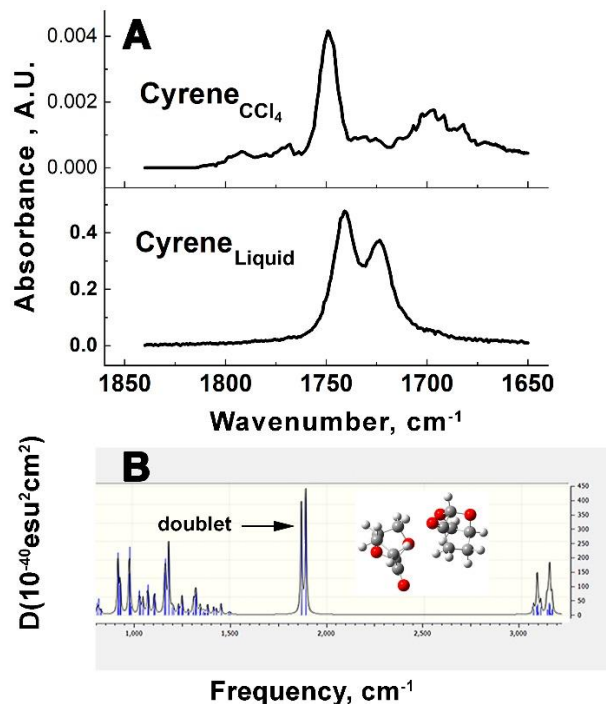


Figure 3. A) A comparison of the FTIR spectra of Cyrene in CCl_4 (upper) with pure liquid Cyrene. B) A simulation of the IR spectrum of one of the six stable conformations of the Cyrene dimer obtained from the DFT calculations. This structure is the second most stable (see SI for further examples).

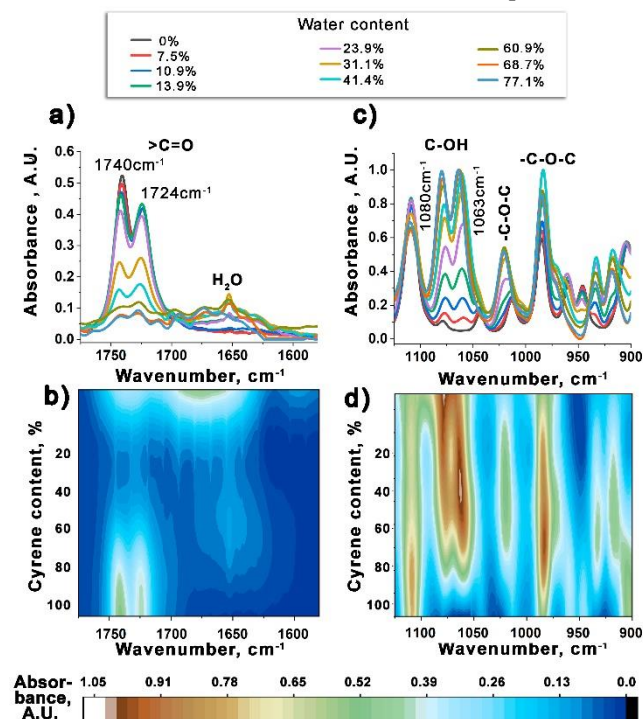


Figure 4. a) and b) Evolution of the carbonyl stretching bands of Cyrene with increasing water content presented as a) a series of one dimensional IR spectra and b) a 2-D IR spectrum. c) and d): Evolution of the C-OH and C-O-C vibrational bands of Cyrene with increasing water content presented as c) a series of one dimensional IR spectra and d) a 2-D IR spectrum.

$$\text{Solubility} = K_1\text{Cy}^2 + K_2\text{Cy} + K_3\text{GDCy} + K_4\text{GD}^2 + K_5\text{GD} + K_6\text{CyH}_2\text{O} + K_7\text{H}_2\text{O} + K_8\text{GDH}_2\text{O}$$

(equation 1)

the concept of micro- heterogeneity proves valuable as the solubilities of all the tested solutes can be described adequately in this way. The amount to which the tested compounds dissolve in a certain micro-environment is thereby proportional to the probability of finding this microcluster in solution. It can be seen that the solubility of the organic substrates around maximum solubilization can always be described as a function of 2-4 main solvent components:

- Cyrene & the 'Cyrene-geminal diol' complex are found to be the main contributors to ibuprofen dissolution;
- Cyrene, Cyrene-water, Cyrene-geminal diol and geminal diol dimer are the main contributors to aspirin dissolution;
- Cyrene, geminal diol and the 'Cyrene-geminal diol' complex for salicylic and ferulic acid dissolution;
- geminal diol (major) and water (minor) for caffeine;
- 'Cyrene-geminal diol' and water (minor) for mandelic acid;

The existence of microheterogeneities in the Cyrene/water/geminal diol mixture was also revealed, somewhat serendipitously, through the behavior of the tetramethylsilane (TMS) reference peak in the ^1H NMR spectra. It can be seen in Figure 6A that for 90-65 wt% Cyrene the TMS peak separates into multiplets. As all of the CH_3 groups (and so all related protons) in TMS are chemically equivalent, this can only be explained if the TMS is experiencing different chemical environments on

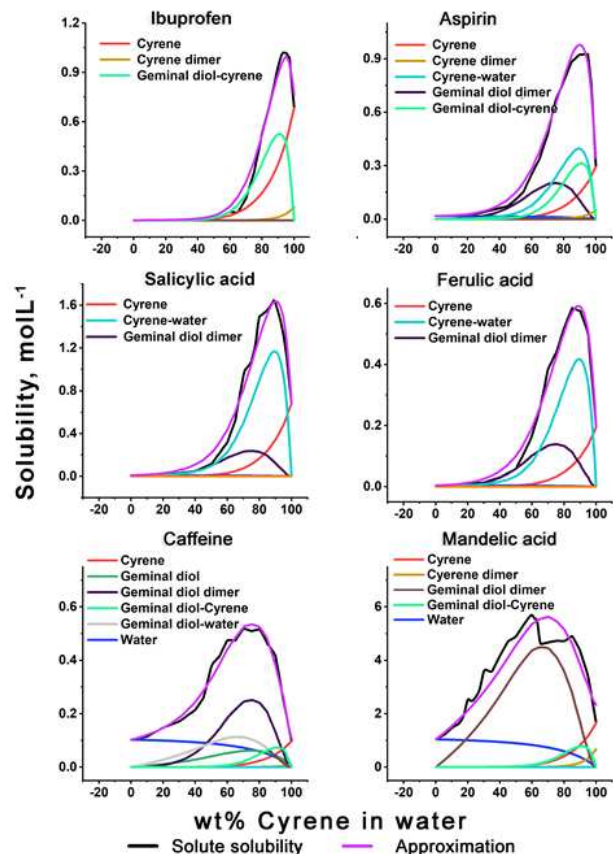


Figure 5 Impact of a range of potential solution components on the solubility of a series of organic compounds as identified by linear regression of the original solubility data

Table 1 Constants obtained for the linear regression analysis of the solubility data

Constants	Solutes					
	Ibuprofen	Aspirin	Salicylic acid	Ferulic acid	Caffeine	Mandelic acid
K	0.08	0.05	0	0	0.01	0.6
1						7
K	0.68	0.29	0.68	0.20	0.10	1.7
2						0
K	7.86	4.68	0	0	1.10	11.
3						7
K	0	5.98	7.02	4.11	7.43	0
4						
K	0	0	0	0	0.34	0
5						
K	0	2.16	6.37	2.28	0	0
6						
K	0.00	0.01	0.00	0.00	0.10	1.0
7	1	7	9	4		4

the molecular level. It is also noteworthy that the ^1H NMR relaxation times of the TMS protons are different for all the observable TMS ^1H NMR peaks, further supporting the presence of microheterogeneities in the Cyrene-water mixture (Figure 6B). To the best of the authors' knowledge, this is unprecedented in the literature. Additionally, the explicit existence of dimeric geminal diol was proven by electrospray mass spectrometry (ESI-MS) as shown in figure 2S. Interestingly, maximum solubility seems to always involve Cyrene's

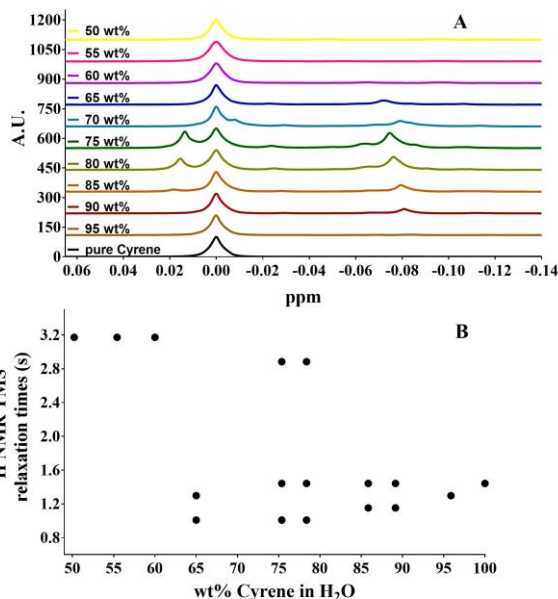


Figure 6 A) appearance of the TMS peak(s) in the ^1H NMR spectra of a range of different Cyrene/water mixtures B) ^1H NMR relaxation times (in seconds) of the TMS protons for the different observable TMS peaks

geminal diol, irrespective of the identity of the solute. It is also noteworthy that we have presently not been able to establish a link between the ranges of maximum dissolution and any physical property of the solutes (e.g. density, viscosity, K_{ow} of the substrates). It could thus be concluded that the observed hydrotrophy is strongly linked to the presence of Cyrene's geminal diol. Tables 3S/4S show that the solubility of all tested compounds increases by a factor of between 4- 100 compared to the solubility in water and between 1.5- 9 times when compared to their solubility in Cyrene.

To date hydrotropic solubilization, *with the occurrence of strong solubility maxima*, has been little reported on. A noteworthy example is the dissolution of lignin monomeric model compounds and technical lignins using aqueous solutions of deep eutectic solvents (DESs).²⁴ Also ionic liquids (ILs) have been shown to function as 'catanionic' hydrotropes when used in an aqueous medium.²⁵ Very recently, Ma et al. published a comprehensive overview on how the addition of water to DESs and ILs affects their properties, behavior and three-dimensional structure.²⁶ Structural organization is long known to exist in urea/water mixtures.²⁷

Importantly, for practical applications (e.g., extractions, isolations) recovery of the substrates can be achieved by shifting the TM-H₂O equilibrium to a zone in which the solute is no longer soluble. This can be realized by adding the necessary amount of water to achieve, for example, a Cyrene concentration below 40 wt%, at which point most of the solutes discussed above are significantly less soluble (Figure 5). The drawback to this procedure is the need to distill out larger amounts of water in order to regain pure Cyrene, which evidently comes at a significant energetic cost. However, for this, *and probably also many other applications*, distillation basically needs to reform only a suitable technical grade of Cyrene *such as 80wt% Cyrene in water*. In cases of poor solute solubility in Cyrene, the use of water as an anti-solvent could be foreseen and the water could be directly distilled out of the mixture. Any recovered water could be re-used to reform the required/desired Cyrene/water mixture and/or as the anti-solvent without extensive purification. A full LCA analysis is currently in progress. Lowering or increasing the temperature may also aid the precipitation process as variable temperature NMR studies of the TM-H₂O equilibrium show that a decrease/increase in temperature favors the geminal diol and Cyrene respectively (Figure 3S_A/B), thus changing the polarity of the overall mixture.

CONCLUSION

In conclusion, this work describes an elegant way to tune the dissolution properties of Cyrene by the addition of water, thus generating a continuum of green solvents with controllable solubilization properties. Central to this is the unique ability of Cyrene to generate significant amounts of Cyrene's geminal diol. In this respect, it is noteworthy that with most ketones in aqueous solutions the ketone/geminal diol equilibrium tends to lie dominantly on the ketone side. Additionally, many ketones are also insoluble in water e.g. cycloheptanone. Cyrene's geminal diol is an amphiphilic molecule, which can act as a switchable and reversible hydrotrope. Solubility increases of up to 100-fold (over water solubility) can be achieved. Examination by linear regression of the solubility profiles of a range of compounds shows that the observed solubility profiles can only

be explained by considering the existence of micro-environments in the TM-H₂O system. The existence of such micro-environments is adequately, and uniquely, proven by FT-IR, DFT, ESI-MS and the variable presence of single or multiple tetramethylsilane peaks in the ¹H NMR spectra of a range of Cyrene/water mixtures. The Cyrene-water solvent mixture is importantly not mutagenic, barely ecotoxic, bio-derived and endowed with tuneable hydrophilic/ hydrophobic properties.

ASSOCIATED CONTENT

Supporting Information. ¹H and ¹³C NMR spectra of Cyrene-water mixtures (inclusive of variable T) and those including solutes; Tabulated solubility values of a range of compounds in Cyrene-water mixtures; Compositional data of the Cyrene/H₂O/geminal diol ternary mixture inclusive of the calculated equilibrium constants; Data on relative solubility increases vis-à-vis water/Cyrene and ranges of maximum solubility. ESI-MS of Cyrene-water. DFT calculations and IR simulations of single/dimeric/trimeric Cyrene. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

* Dr. Mario De bruyn, debruyn@wisc.edu

Author Contributions

M.D.b., V.L.B. and A.M. conceived the different ideas/approaches and were the main experimental contributors. S.S. as an expert in hydrotrophy and, A.J.H. as an expert in solvents, gave valuable background information, in addition to supervising and providing scientific input on the work of A.M. H.F. and H.H. assisted with NMR experimentation. M.C. performed all of the DFT calculations and produced the simulated IR spectra. J.H.C., D.J.M. and B.M.W. gave valuable scientific, background and redaction advice. The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Funding Sources

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 701028.

ACKNOWLEDGMENT

MDb acknowledges the European Union's Horizon 2020 research and innovation programme under grant agreement No. 701028 (EU Marie Curie Global Fellowship). We would like to also acknowledge the Circa Company, and especially Dr Warwick Raverty and Mr Tony Duncan for the kind and regular provision of double distilled dihydrolevoglucosenone. We thank the UW-Madison Department of Chemistry for the use of a Bruker Avance 500 MHz NMR Spectrometer; a generous gift from Paul J. Bender enabled purchase of this spectrometer in 2012. AJH would like to thank the Center of Excellence for Innovation in Chemistry (PERCH-CIC).

-
1. Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Sherwood, J., Opportunities for Bio-Based Solvents Created as Petrochemical and Fuel Products Transition towards Renewable Resources. *Int J Mol Sci* **2015**, *16* (8), 17101-17159, DOI 10.3390/ijms160817101
 2. Abbott, S.; Booth, J. J.; Shimizu, S., Practical molecular thermodynamics for greener solution chemistry. *Green Chem* **2017**, *19* (1), 68-75, DOI 10.1039/C6GC03002E
 3. Kunz, W.; Holmberg, K.; Zemb, T., Hydrotropes. *Curr Opin Colloid In* **2016**, *22*, 99-107, DOI 10.1016/j.cocis.2016.03.005
 4. F.P. Byrne, S. J., G. Paggiola, T.H.M. Petchey, J.H. Clark, T.J. Farmer, A.J. Hunt, C.R. McElroy, J. Sherwood, Tools and techniques for solvent selection: green solvent selection guides. *Sustainable Chemical Processes* **2016**, *4* (7), DOI 10.1186/s40508-016-0051-z
 5. Candidate List of substances of very high concern for Authorisation. (ECHA), E. C. A., Ed.
 6. Sherwood, J., European Restrictions on 1,2-Dichloroethane: C-H Activation Research and Development Should Be Liberated and not Limited. *Angew Chem Int Edit* **2018**, *57* (43), 14286-14290, DOI 10.1002/anie.201800549
 7. Gu, Y. L.; Jerome, F., Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry. *Chem Soc Rev* **2013**, *42* (24), 9550-9570, DOI 10.1039/C3CS60241A
 8. Sherwood, J.; De Bruyn, M.; Constantinou, A.; Moity, L.; McElroy, C. R.; Farmer, T. J.; Duncan, T.; Raverty, W.; Hunt, A. J.; Clark, J. H., Dihydrolevoglucosenone (Cyrene) as a bio-based alternative for dipolar aprotic solvents. *Chem Commun* **2014**, *50* (68), 9650-9652, DOI 10.1039/C4CC04133J
 9. Zhang, J. F.; White, G. B.; Ryan, M. D.; Hunt, A. J.; Katz, M. J., Dihydrolevoglucosenone (Cyrene) As a Green Alternative to N,N-Dimethylformamide (DMF) in MOF Synthesis. *Acs Sustain Chem Eng* **2016**, *4* (12), 7186-7192, DOI 10.1021/acssuschemeng.6b02115
 10. Santoro, S.; Ferlin, F.; Luciani, L.; Ackermann, L.; Vaccaro, L., Biomass-derived solvents as effective media for cross-coupling reactions and C-H functionalization processes. *Green Chem* **2017**, *19* (7), 1601-1612, DOI 10.1039/C7GC00067G
 11. Mendes-Jorge, B., Circa receives green light to sell non-toxic, bio-based and biodegradable solvent in EU. Sustainability Consult: 2019.
 12. Boelo Schuur, T. B., Dion Smink and Lisette M. J. Sprakel, Green solvents for sustainable separation processes. *Current Opinion in Green and Sustainable Chemistry* **2019**, *18*, 57-65, DOI 10.1016/j.cogsc.2018.12.009
 13. Sheldon, R. A., The greening of solvents: Towards sustainable organic synthesis. *Current Opinion in Green and Sustainable Chemistry* **2019**, *18*, 13-19, DOI 10.1016/j.cogsc.2018.11.006
 14. Clarke, C. J.; Tu, W. C.; Levers, O.; Brohl, A.; Hallett, J. P., Green and Sustainable Solvents in Chemical Processes. *Chem Rev* **2018**, *118* (2), 747-800, DOI 10.1021/acs.chemrev.7b00571
 15. Molinier, V.; Aubry, J. M., Sugar-based hydrotropes: preparation, properties and applications. *Spr Carb Ch* **2014**, *40*, 51-72, DOI 10.1039/9781849739986-00051
 16. Hodgdon, T. K.; Kaler, E. W., Hydrotropic solutions. *Curr Opin Colloid In* **2007**, *12* (3), 121-128, DOI 10.1016/j.cocis.2007.06.004
 17. Subbarao, C. V.; Chakravarthy, I. P. K.; Bharadwaj, A. V. S. L. S.; Prasad, K. M. M. K., Functions of Hydrotropes in Solutions. *Chem Eng Technol* **2012**, *35* (2), 225-237, DOI 10.1002/ceat.201100484
 18. Thakker, M. R.; Parikh, J. K.; Desai, M. A., Ultrasound Assisted Hydrotropic Extraction: A Greener Approach for the Isolation of Geraniol from the Leaves of *Cymbopogon martinii*. *Acs Sustain Chem Eng* **2018**, *6* (3), 3215-3224, DOI 10.1021/acssuschemeng.7b03374
 19. Hatzopoulos, M. H.; Eastoe, J.; Dowding, P. J.; Rogers, S. E.; Heenan, R.; Dyer, R., Are Hydrotropes Distinct from Surfactants? *Langmuir* **2011**, *27* (20), 12346-12353, DOI 10.1021/la2025846

20. Booth, J. J.; Omar, M.; Abbott, S.; Shimizu, S., Hydrotrope accumulation around the drug: the driving force for solubilization and minimum hydrotrope concentration for nicotinamide and urea. *Phys Chem Chem Phys* **2015**, *17* (12), 8028-8037, DOI 10.1039/c4cp05414h
21. Shimizu, S.; Matubayasi, N., The origin of cooperative solubilisation by hydrotropes. *Phys Chem Chem Phys* **2016**, *18* (36), 25621-25628, DOI 10.1039/C6CP04823D
22. Rooney, J. J., A Simple Statistical Mechanical Rationale of Trouton Rule. *P Roy Irish Acad B* **1988**, *88* (3), 39-43.
23. Degen, I. A., *Tables of Characteristic Group Frequencies for the Interpretation of Infrared and Raman Spectra*. Harrow: Acolyte Publ: 1997.
24. Soares, B.; Tavares, D. J. P.; Amaral, J. L.; Silvestre, A. J. D.; Freire, C. S. R.; Coutinho, J. A. P., Enhanced Solubility of Lignin Monomeric Model Compounds and Technical Lignins in Aqueous Solutions of Deep Eutectic Solvents. *Acs Sustain Chem Eng* **2017**, *5* (5), 4056-4065, DOI 10.1021/acssuschemeng.7b00053
25. Claudio, A. F. M.; Neves, M. C.; Shimizu, K.; Lopes, J. N. C.; Freire, M. G.; Coutinho, J. A. P., The magic of aqueous solutions of ionic liquids: ionic liquids as a powerful class of cationic hydrotropes. *Green Chem* **2015**, *17* (7), 3948-3963, DOI 10.1039/C5GC00712G
26. Ma, C. Y.; Laaksonen, A.; Liu, C.; Lu, X. H.; Ji, X. Y., The peculiar effect of water on ionic liquids and deep eutectic solvents. *Chem Soc Rev* **2018**, *47* (23), 8685-8720, DOI 10.1039/C8CS00325D
27. Frank, H. S.; Franks, F., Structural Approach to Solvent Power of Water for Hydrocarbons - Urea as a Structure Breaker. *J Chem Phys* **1968**, *48* (10), 4746-4757, DOI 10.1063/1.1668057



Addition of water to Cyrene generates a continuum of green solvents with controllable solubilization properties centered on Cyrene's geminal diol. The solvent is non-mutagenic, barely ecotoxic and bio-derived.