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Dihydrolevoglucosenone (Cyrene) as a bio-based alternative for dipolar aprotic solvents†

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Dihydrolevoglucosenone (Cyrene) is a bio-based molecule, derived in two simple steps from cellulose, which demonstrates significant promise as a dipolar aprotic solvent. The dipolarity of dihydrolevoglucosenone is similar to NMP, DMF and sulpholane. Dihydrolevoglucosenone demonstrates similar performance to NMP in a fluorination reaction and the Menschutkin reaction.

Solvents are ubiquitous throughout the chemical industry. In recent times environmental health and safety concerns and stricter legislation have created an interest in greener solvents.[1] Within the fine chemical industry, existing organic solvents could be directly substituted for greener alternatives with similar properties yet preferably derived from a renewable feedstock as part of a solvent replacement strategy.[2]

Typical examples of bio-based solvents include protic compounds such as bio-ethanol and glycerol,[3] and 2-methyltetrahydrofuran as a medium polarity solvent.[4] Terpenes and their derivatives have also been proven as valuable bio-based hydrocarbon solvents.[5] However few bio-derived solvent solutions have been established as replacements for highly dipolar aprotic solvents, yet it is these solvents that are currently the subject of considerable attention under REACh and other chemical legislation. *N*-Methylpyrrolidinone (NMP) for example, which is widely used in chemical and pharmaceutical processing and in formulations, is on the European candidate list of substances of very high concern due to its toxicity.[6,7]

Herein is evidence that levoglucosenone, which can be made in a single step from biomass (cellulose),[8] can be readily hydrogenated to dihydrolevoglucosenone, hence named "Cyrene", which is able to serve as a bio-based substitute for toxic petrochemical-derived solvents such as NMP (Fig. 1). The renewable nature of dihydrolevoglucosenone makes it particularly attractive especially as regions such as the EU are encouraging a bio-based economy including the production and use of chemicals from biomass. Concerning the hydrogenation of levoglucosenone, at present hydrogen is predominantly generated through steam reforming of natural gas,[9] as electrolysis from water using renewable energy is not yet economically viable.[10] There are however numerous studies into sustainable hydrogen generation and it is conceivable that a competitive and renewable source of H_2 will be available in the near future.[11]

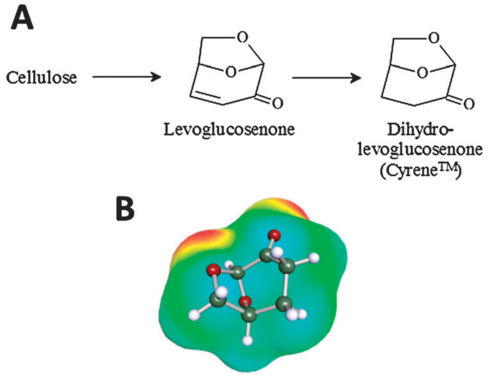

Fig. 1 (A) Scheme for the production of dihydrolevoglucosenone (Cyrene) and (B) σ-surface (COSMO surface) of dihydrolevoglucosenone.

The hydrogenation of levoglucosenone over supported palladium catalysts has been reported before and is highly selective (yield $>$ 90%).[12] While originally performed in an excess of ethyl acetate it was found that the quantity of solvent could be greatly reduced at the expense of suppressing the reaction rate (see ESI†). Conducting the reaction at higher hydrogen pressures (3–80 bar) allowed for greater reaction rates without affecting selectivity. It was also found possible to conduct this room temperature hydrogenation in the absence of an auxiliary solvent. This solvent-free reaction proceeds best using higher hydrogen pressures, again with no loss of selectivity. The possibility to perform this reaction in the absence of a solvent imparts significant economic advantages and makes the commercialisation of Cyrene as a solvent viable. The high stability of the cyclic acetal in dihydrolevoglucosenone relates to a

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double anomeric effect due to the fused ring system, moreover acetal groups are known to be stable towards bases and nucleophiles. A preliminary Ames mutagenicity screening has been completed on Cyrene with no mutagenicity observed.

It is crucial that the polarity profile of prospective solvents is known in order to correctly assign suitable applications for them. Dihydrolevoglucosenone has been modelled using full DFT/COSMO geometry optimisations that describe a discrete surface around dihydrolevoglucosenone embedded in a perfect virtual conductor, the so-called σ-surface (as generated *via* COSMOtherm, see Fig. 1).[13] This surface shows the charge density distribution of dihydrolevoglucosenone: green to yellow corresponds to weakly polar surfaces, while red represents a strongly negative charge density and blue a positive charge density. The distinct dipoles suggest dihydrolevoglucosenone may behave similarly to conventional dipolar aprotic solvents if used as a reaction medium.

The Kamlet–Abboud–Taft parameters were also obtained.[14] These indicate that dihydrolevoglucosenone is aprotic with a similar π^* value (corresponding to dipolarity) to those of highly dipolar aprotic solvents, but with a slightly lower β value which is an indicator of hydrogen bond accepting ability (Table 1). Consequently dihydrolevoglucosenone is one of only a few solvents with the potential to offer an alternative to the traditional dipolar aprotic solvents. This observation is made more remarkable by the fact that the molecule does not contain nitrogen and sulphur heteroatoms as typically found in polar aprotic solvents. Avoidance of these heteroatoms is beneficial as they are known to lead to atmospheric pollution when the solvent is incinerated.[15]

Whereas the Kamlet–Abboud–Taft polarity scales are useful in correlations with reaction kinetics and equilibria, the Hansen solubility parameters provide a measure of solvency power.[16] In this approach, solvents are located in the "Hansen space", a three-dimensional representation of dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h) interactions (combined these intermolecular forces express the Hildebrand parameter). The closer two solvents are in the Hansen space, the more likely they are to exhibit the same solubilising properties. Dihydrolevoglucosenone has been mapped in the Hansen space and compared to classical organic solvents (see Fig. S7 of the ESI†). Considering all three parameters, the closest solvent match to Cyrene is NMP (Table 1).

The boiling point of dihydrolevoglucosenone was determined using TGA under a low nitrogen flow, to give a value of approximately 203 °C. This figure is similar to a predicted boiling point of 194 °C (HSPiP) although more precise analysis is ongoing. The density of dihydrolevoglucosenone as determined experimentally is 1.25 g mL^{-1} at 293 K.

Two substitution reactions with special importance to the pharmaceutical and agrochemical industries (which are major users of dipolar aprotic solvents like NMP) were used to evaluate the solvent performance of dihydrolevoglucosenone in relation to other established solvents. The Menschutkin reaction is an alkylation reaction that progresses *via* a S_N2 mechanism. It is now the basis for the synthesis of imidazolium ionic liquids.[21] More generally, heteroatom alkylation is the most prevalent reaction performed in the pharmaceutical industry,[22] meaning the synthesis of 1-decyl-2,3-dimethylimidazolium bromide from 1,2-dimethylimidazole and 1-bromodecane is an appropriate generalised case study in the assessment of Cyrene as a bio-based solvent (Fig. 2). The rate of this reaction has been established as being proportional to the dipolarity of the solvent, with protic solvents suppressing the reaction rate.[23] A linear solvation energy relationship (LSER) is used to quantify this type of empirical relationship (Fig. 2).[24] It shows dihydrolevoglucosenone as one of the best solvents for this reaction, outperforming most other dipolar aprotic solvents (*e.g.* dioxane, DMF, DMAc and NMP) and only slightly inferior to sulphur-containing DMSO and sulpholane in a comparison of experimental rate constants.

In addition a model fluorination reaction was investigated (Fig. 2). Fluorination is highly relevant to the pharmaceutical industry, and new greener methods for conducting this type of reaction are of significant commercial interest.[25] Of the top 200 drugs as gauged by US retail sales in 2012, over 15% contain fluorine.[26] The simplest method of introducing fluorine into an aromatic molecule is *via* a S_NAr reaction, where the rate of reaction is dependent on the stabilisation afforded to the Meisenheimer intermediate, but meanwhile not deactivating the fluoride nucleophile.[27] This role is typically fulfilled by conventional dipolar aprotic solvents, and as such dihydrolevoglucosenone would offer an interesting alternative reaction medium.

The rate of the fluorination is strongly dependent on the dipolarity (π^*) of the solvent. Outside of a small domain of highly dipolar aprotic solvents, the rate of observable fluorination falls to negligible levels. Dihydrolevoglucosenone was found to possess the correct attributes to promote the reaction, albeit providing the slowest kinetics of those solvents successfully tested. As in the

Table 1 Physical properties of selected dipolar aprotic solvents

	Cyrene	NMP	Cyclohexanone	DMF	DMAc	DMSO	Sulpholane
E_T^N	0.333	0.355[17]	0.281[17]	0.386[17]	0.377[17]	0.444[17]	0.410[17]
α	0.00	0.00	0.00[5]	0.00[18]	0.00[18]	0.00[18]	0.00
β	0.61	0.75	0.58[5]	0.71[19]	0.73[19]	0.74[19]	0.30
π^*	0.93	0.90	0.71[5]	0.88[19]	0.85[19]	1.00[19]	0.96
δ_D/MPa$^{0.5}$	18.8[a]	18.0[16]	17.8[16]	17.4[16]	16.8[16]	18.4[16]	20.3[16]
δ_P/MPa$^{0.5}$	10.6[a]	12.3[16]	6.3[16]	13.7[16]	11.5[16]	16.4[16]	18.2[16]
δ_H/MPa$^{0.5}$	6.9[a]	7.2[16]	5.1[16]	11.3[16]	10.2[16]	10.2[16]	10.9[16]
BP/°C	203	202[1]	155[1]	153[1]	165[1]	189[1]	282[1]
ρ/g mL^{-1}	1.25	1.03[20]	0.95	0.94[20]	0.94[20]	1.10[20]	1.26[20]

[a] Calculated with HSPiP software.

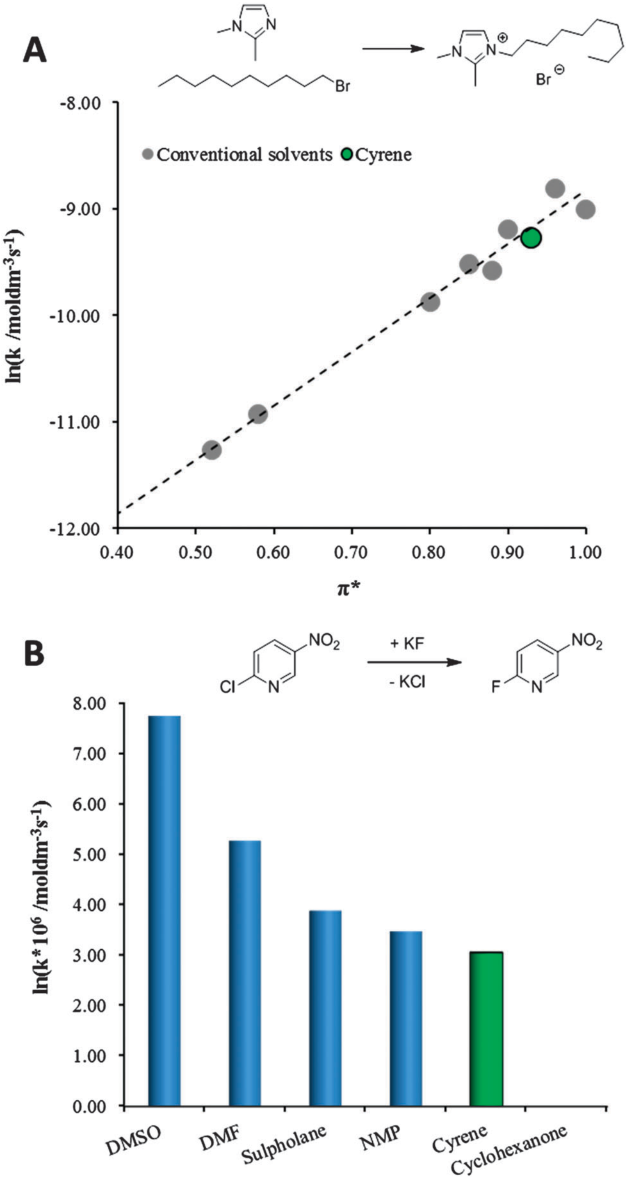

Fig. 2 (A) A LSER of the Menschutkin reaction and (B) rates of fluorination in different solvents.

Menschutkin reaction, dihydrolevoglucosenone was found to match the performance of NMP.

Dihydrolevoglucosenone (Cyrene) is a new and very promising bio-based solvent substitute for widely used dipolar aprotic solvents (*e.g.* NMP) that are increasingly under threat from chemical legislation such as REACh. Dihydrolevoglucosenone can be made in two simple steps from biomass ensuring a low environmental footprint as well as economic viability. Currently, work is in progress to make the hydrogenation process more sustainable by replacing precious palladium by other non-critical transition metals. The solvent properties of dihydrolevoglucosenone are very similar to NMP, but in the absence of nitrogen or sulphur heteroatoms which lead to NO_x and SO_x emissions upon incineration, end-of-life environmental concerns are reduced.

Heteroatom alkylations and nucleophilic fluorinations are two commonly used reactions in the pharmaceutical and other high-value chemical manufacturing sectors. Both types of reaction can be carried out in dihydrolevoglucosenone with minimal losses in performance compared to traditional but non-renewable alternatives. Additional testing of dihydrolevoglucosenone and other derivatives of levoglucosenone is being conducted to further understand the capacity of these bio-based solvents to replace NMP and similar solvents in synthetic chemistry and other applications.

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Notes and references

1 P. G. Jessop, *Green Chem.*, 2011, **13**, 1391; C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927; R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, *Green Chem.*, 2011, **13**, 854.
2 Y. Gu and F. Jérôme, *Chem. Soc. Rev.*, 2013, **42**, 9550.
3 Y. Gu and F. Jérôme, *Green Chem.*, 2010, **12**, 1127.
4 D. F. Aycock, *Org. Process Res. Dev.*, 2007, **11**, 156.
5 J. H. Clark, D. J. Macquarrie and J. Sherwood, *Green Chem.*, 2012, **14**, 90; J. H. Clark, D. J. Macquarrie and J. Sherwood, *Chem. – Eur. J.*, 2013, **19**, 5174; G. Paggiola, A. J. Hunt, C. R. McElroy, J. Sherwood and J. H. Clark, *Green Chem.*, 2014, **16**, 2107.
6 G. M. Solomon, E. P. Morse, M. J. Garbo and D. K. Milton, *J. Occup. Environ. Med.*, 1996, **38**, 705–713.
7 European Chemicals Agency (ECHA), Candidate list of substances of very high concern for authorisation, available online at http://echa.europa.eu/candidate-list-table. Accessed 17/02/2014.
8 K. Koseki, T. Ebata, H. Kawakami, H. Matsushita, K. Itoh and Y. Naoi, *US Pat.*, 5,112,994, 1992.
9 A. L. Dicks, *J. Power Sources*, 1996, **61**, 113.
10 C. Lamy, *Waste Gas Treatment for Resource Recovery*, IWA Publishing, London, 2006.
11 P. Panagiotopoulou, C. Papadopoulou, H. Matralis and X. Verykios, *Wiley Interdiscip. Rev.: Energy Environ.*, 2014, **3**, 213; C. Cormos, *Int. J. Hydrogen Energy*, 2014, **39**, 5597; S. Rau, S. Vierrath, J. Ohlmann, A. Fallisch, D. Lackner, F. Dimroth and T. Smolinka, *Energy Technol.*, 2014, **2**, 43.
12 G. R. Court, C. H. Lawrence, W. D. Raverty and A. J. Duncan, *US Pat.*, 2012/0111714 A1, 2012.
13 A. Klamt and G. Schuurmann, *J. Chem. Soc., Perkin Trans. 2*, 1993, 799–805.
14 M. J. Kamlet, J. L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.*, 1983, **48**, 2877; P. G. Jessop, D. A. Jessop, D. Fu and L. Phan, *Green Chem.*, 2012, **14**, 1245.
15 A. D. Curzons, D. C. Constable and V. L. Cunningham, *Clean Prod. Processes*, 1999, **1**, 82.
16 C. M. Hansen, *Hansen Solubility Parameters: A User's Handbook*, CRC Press, Boca Raton, 2nd edn, 2007.
17 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, 3rd edn, 2003.
18 Y. Marcus, *Chem. Soc. Rev.*, 1993, **22**, 409.
19 M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 377.
20 U. Tilstam, *Org. Process Res. Dev.*, 2012, **16**, 1273.
21 J. C. Schleicher and A. M. Scurto, *Green Chem.*, 2009, **11**, 694.
22 T. W. J. Cooper, I. B. Campbell and S. J. F. MacDonald, *Angew. Chem., Int. Ed.*, 2010, **49**, 8082; J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337; R. W. Dugger, J. A. Ragan and D. H. B. Ripin, *Org. Process Res. Dev.*, 2005, **9**, 253.
23 M. H. Abraham, *Chem. Commun.*, 1969, 1307.
24 R. W. Taft, J. –L. M. Abboud, M. J. Kamlet and M. H. Abraham, *J. Solution Chem.*, 1985, **14**, 153.
25 S. J. Tavener and J. H. Clark, *J. Fluorine Chem.*, 2003, **123**, 31.
26 Jón Njaðarson research group website, *Top 200 Pharmaceutical Products by US Retail Sales in* 2012, available online at http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster, Accessed 17/02/2014; N. A. McGrath, M. Brichace and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348.
27 J. H. Clark and D. J. Macquarrie, *J. Fluorine Chem.*, 1987, **35**, 591.