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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 has created an interest in greener solvents. 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.

Typical examples of bio-based solvents include protic compounds such as bio-ethanol and glycerol, and 2-methyltetrahydrofuran as a medium polarity solvent. Terpenes and their derivatives have also been proven as valuable bio-based hydrocarbon solvents. 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. Herein is evidence that levoglucosenone, which can be made in a single step from biomass (cellulose), 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 (Figure 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, as electrolysis from water using renewable energy is not yet economically viable. There are however numerous studies into sustainable hydrogen generation and it is conceivable that a competitive and renewable source of H2 will be available in the near future.

The hydrogenation of levoglucosenone over supported palladium catalysts has been reported before and is highly selective (yield > 90%). 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 Supplementary Information). 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 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 describes a discrete surface around dihydrolevoglucosenone embedded in a perfect virtual conductor, the so-called σE-surface (as generated via COSMOTHERM, see Figure 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–Abbud–Taft parameters were also obtained.[14] These indicate that dihydrolevoglucosenone is aprotic with a similar πE* 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–Abbud–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 (δE), polar (δP) and hydrogen bonding (δH) 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 Figure S7 of the Supplementary Information). 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 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 S22 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 4-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 (Figure 2). The rate of this reaction has been established being as 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 (Figure 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 sulfolane in a comparison of experimental rate constants.

In addition a model fluorination reaction was investigated (Figure 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 a molecule is via a S35Ar reaction, where the rate of reaction is dependent on the stabilisation afforded to the

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Table 1 Physical properties of selected dipolar aprotic solvents.

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<tr>
<th>Solvent</th>
<th>Cyrene</th>
<th>NMP</th>
<th>Cyclohexanone</th>
<th>DMF</th>
<th>DMac</th>
<th>DMSO</th>
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*a calculated with HSPiP software
Meisenheimer intermediate, but meanwhile not deactivating the fluoride nucleophile. 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 was found to match the performance of NMP.

As in the Menschutkin reaction, dihydrolevoglucosenone would offer an interesting alternative reaction medium. 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 Menschutkin reaction, dihydrolevoglucosenone was found to match the performance of NMP.

**Figure 2** A) A LSER of the Menschutkin reaction and B) Rates of fluorination in different solvents.

**Conclusions**

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 helping ensure 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 leading to NOx and SOx 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.

**Acknowledgements**

The Authors would like to thank Circa Group for the supply of levoglucosenone and for financial support of the research.

**Notes and references**


26 Jón Njardarson 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.