Journal Name

ARTICLE

Received 00th January 20xx,

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Challenges in the development of bio-based solvents: a case study on methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate as an alternative aprotic solvent

Saimeng Jin,[a] Fergal Byrne,[a] Con Robert McElroy,[a] James Sherwood,[a] James H. Clark[a] and Andrew J. Hunt[a]*

Many traditional solvents have drawbacks including sustainability and toxicity issues. Legislations such as REACH is driving the move towards less hazardous chemicals and production processes. Therefore, safer bio-based solvents need to be developed. Herein, a 10 step method has been proposed for the development of new bio-based solvents that utilise a combination of in silico modelling of Hansen solubility parameters (HSPs), experimental Kamlet-Abboud-Taft parameters, selection of green synthetic routes followed by applications testing and toxicity measurements. The challenges that the chemical industry face in the development of new bio-based solvents are highlighted through a case study on methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC) which can be synthesised from glycerol. Although MMC is an attractive candidate as a replacement solvent, simply being bio-derived is not enough for a molecule to be regarded as green. The methodology of solvent development described here is a broadly applicable protocol that will indicate if a new bio-based solvent is functionally proficient, but will also highlight the importance of early stage Kamlet-Abboud-Taft parameters determination and toxicity testing in the development of a green solvent.

Introduction

Solvents are commonly applied in large volumes in industrial and lab-based procedures as a reaction medium in addition to their use for extraction, separation and purification.[1,2] In 2012, global consumption of solvent was about 28 million tonnes.[3] Despite their large scale use, issues relating to their environmental impact, health, safety and sustainability remain. Many traditional organic solvents are toxic, while some halogenated solvents have been shown to deplete the ozone layer.[4] Furthermore, most conventional organic solvents are non-renewable and therefore at odds with the principles of sustainable development.[5]

Since 2006, European Regulation (EC) No 1907/2006 "Registration, Evaluation, Authorisation and restriction of Chemicals" (REACH) has been influencing the chemical market within the EU.[6] REACH obliges companies to register and provide comprehensive physical properties, toxicological data and environmental data for every chemical that is manufactured or imported in quantities of one tonne or more per year ("no data, no market"). The REACH authorisation process can place a substance on a list of Substances of Very High Concern (SVHC).[7] This list includes traditional solvents such as 1-methyl-2-pyrrolidone (NMP), *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMAc). The sale and use of each SVHC will be restricted or effectively prohibited. Restrictions are already in place for many hazardous substances including the widely used conventional solvents dichloromethane (DCM), chloroform, benzene and toluene.[8] Any products containing inappropriate substances as defined by REACH will be eliminated from the market by the 'Rapid Alert System for Dangerous Non-food Products' (RAPEX) information scheme.[9] Outside of Europe, other laws including Schedule I of the "Canadian Environmental Protection Act", in Canada,[10] and "Code of Federal Regulation Title 40", in the USA,[11] also limit the use of toxic substances. In order to avoid the issues of traditional solvents and abide by relevant legislation, it is important to intelligently develop REACH compliant substitutes to conventional solvents while retaining their desirable properties.

The challenge for developing bio-based solvents

Bio-based solvents have been identified as green candidates to replace petroleum-derived solvents.[12,13] The benefit of bio-based solvents is that they are renewable and potentially do not result in a net increase of carbon dioxide in the atmosphere at the end of their lifetimes. Up to now, a number of bio-based solvents such as dihydrolevoglucosenone (Cyrene™),[14] *p*-cymene,[15] 2-methyltetrahydrofuran (2-MeTHF),[16] d-limonene,[17] ethyl lactate,[18] and *γ*-valerolactone

Green Chemistry Centre of Excellence, Department of Chemistry, The University of York, Heslington, York, YO10 5DD, UK., Tel: +44(0)1904324456, E-mail: andrew.hunt@york.ac.uk

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

(GVL)[19] have been developed. Despite their advantages, bio-based solvents are not necessarily safer, less toxic, or more environmentally benign compared to conventional solvents and so full analysis must be carried out before they can be classified as green. Some of the main challenges in the development of bio-based solvents are data availability (physical properties and toxicity), performance and cost. Bio-based solvents offer the opportunity to develop renewable and sustainable alternatives to traditional petrochemical-derived solvents. The EU will shortly ratify the European bio-based solvent standard, which will set out the requirements for these solvents in terms of properties, limits, application classes and test methods.[20] It details for assessment and standardises the determination of bio-based content for these molecules. Such standards for solvents will aid to increase the development of this important class of bio-based products.

Herein, a methodology has been proposed to develop new bio-based solvents based on our understanding of the challenges involved (Figure 1). The methodology of solvent testing described here is a broadly applicable protocol that will indicate if a new solvent is functionally proficient (through a combination of in silico modelling, property measurements and lab scale testing), but will also highlight potential health risk of the solvent under investigation. The combination of such a methodology and the use of the European bio-based solvent standard will be a powerful tool for bio-based solvent development. This method is then applied to the development stages of a bio-based solvent, methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC), in a case study. Recently, MMC was synthesised in two steps from glycerol and was reported to be green due to the renewable nature of the feedstock and the clean synthetic methods used in its synthesis.[21] Herein, the synthesis of MMC was optimised and in silico modelling of Hansen solubility parameters relating to dispersion (δD), polar (δP) and hydrogen bonding (δH) interactions predicted that MMC would be an attractive candidate for use as an alternative bio-based aprotic solvent. Kamlet–Abboud–Taft (KAT) polarity scale measurements confirmed that this solvent has properties between dichloromethane, acetone and ethyl acetate. Testing of this solvent demonstrated MMC as a suitable solvent for both the Friedel-Crafts and Diels-Alder reactions.

Step 1: Define the polarity and physical properties of solvent to be replaced

Solvents are selected based on their favourable properties, usually volatility, polarity and flammability. Their negative properties, such as toxicity and environmental hazards, are a consequence of their chemical structure but need not go hand in hand. If the valuable attributes of a solvent can be understood and defined, solvent substitution can be executed more effectively by eliminating the negative properties. The boiling point, melting point, density and flammability properties of traditional solvents are widely available. However, polarity is often an important property for a solvent and is potentially responsible for improving reaction rates, along with equilibria, solubility, cleaning or extraction efficiency. A solvent polarity map is a convenient tool during the first step of solvent selection. It gives a visual representation of the polarity of the solvent to be replaced and can be used to easily identify other solvents with similar polarity.

The Kamlet-Abboud-Taft (KAT) solvatochromic parameters are widely used as a tool for understanding solvent polarity. The KAT parameters consist of α (hydrogen bond donating ability),[22] β (hydrogen bond accepting ability)[23] and π* (dipolarity).[24] A two-dimensional KAT solvent plot (map) can be then established with β represented on the y-axis and π* on the x-axis. The contribution of α is recognised by employing two maps, one for protic solvents (with α higher than 0.5), and another for aprotic solvents (with α lower than 0.5). Solvents which are in close proximity to one another on the solvent map are likely to have similar solvent properties, especially in reaction chemistry. An example of a KAT solvent map of aprotic solvents, both conventional and bio-based, can be seen in Figure 2. The solvent data shown is indicative, and far from exhaustive.[25]

Step 2: Identify substitute solvents

In this step, the availability of potential solvents, bio-based or fossil derived, is deduced, also using a solvent polarity map. A comparison of physical properties (should they be known) to the ideal characteristics can be similarly made. However, it is not always the case that an obvious and readily available candidate for solvent substitution will be available. In such an instance, a bespoke synthesis of a new solvent maybe required. Although the effort needed is substantial, designing a benign solvent to excel in a particular application is rewarding in the long run. However, the end product must be suitable from a performance, toxicity, environmental and economic perspective. Applying the following steps can help guide this process, but first one must propose molecules that could fulfil the requirements which are currently satisfied by the solvent destined for substitution. This could be speculative, but better still is the use of computer programs that generate solvent candidates based on physical property requirements,[26–28] or available transformation of a bio-based platform molecule.[29,30]

Step 3: *In silico* modelling of candidate solvents

It is vital to calculate the properties of potential bio-based solvents before synthesis in order to fast screen through all promising candidates. The Hansen solubility parameters have been employed for over five decades to measure solvation power, and are amongst the most valuable solvent properties that can be accurately predicted.[31,32] The Hansen solubility parameters are three different scales: δ_D (dispersion forces), δ_P (dipole forces) and δ_H (hydrogen bonding forces). They can be used to construct the three-dimensional Hansen space, in effect another type of polarity map. The distance between two solvents, R_a, in the Hansen space is defined in eqn (1) below:

$$(1) \quad R_a = \sqrt{4(\delta_{D2} - \delta_{D1})^2 + (\delta_{P2} - \delta_{P1})^2 + (\delta_{H2} - \delta_{H1})^2}$$

Generally, if the R_a value between two solvents is low, they are likely to have similar solvency power and dissolve the same types of solute. 'Hansen Solubility Parameters in Practice' (HSPiP, 4th Edition 4.1.04) is a computer program which can be utilised as a powerful tool to predict Hansen solubility parameters.[33] HSPiP can generate the 3D Hansen space and calculate the R_a value between different solvents. As such it assists users in their comparison of solvent candidates with traditional solvents, and can be applied to postulated molecules as well as 'real' solvents.

Step 4: Selection of synthetic pathway to candidate solvent

Once a target molecule has been identified, a synthetic route must be devised. To meet the most stringent definition of "bio based" in relation to a solvent, the raw material must be from biomass, most likely an established platform molecule.[34] A detailed study of the literature will generate numerous potential routes from raw material(s) to product and the greenest of which must be selected. Applying green chemistry principals in route selection is not facile, requiring a fair and holistic methodology that can be easily applied using the data at hand and in a convenient time frame. This is best achieved using a metrics toolkit such as that developed for the pharmaceutical industry.[35]

Step 5: Optimisation of solvent synthesis

The devised synthetic pathway to the target compound must then be applied in practice. Literature precedents are more than likely based on shared functionality as opposed to the reactants selected and therefore may not work or require optimisation. Green chemistry principles must also be applied when changing reaction time, temperature, catalyst, loading, solvent, etc. This would most likely be through monitoring using the same metrics from the step 4. Sufficient solvent needs to be synthesised at the desired purity to allow for full characterisation and application testing. This could be up to 1 L or even more, although a batch-wise synthesis might be necessary at first.

Step 6: Defining physical properties of the solvent

In order for a solvent to be applied, various physical and solubility properties must be first defined. For a formal list of solvent requirements, the European technical specification for bio-based solvents is helpful (CEN/TS 16766:2015).[20] There are no thresholds to define what physical properties are acceptable, only that the data is presented in a certain way, according to specific test methods. The mandatory solvent characteristics that must be known to adhere to CEN/TS 16766:2015 are composition (for formulations), polarity (Hansen solubility parameters), boiling point, vapour pressure or evaporation rate, colour, density, and viscosity. The one requirement in CEN/TS 16766:2015 that does employ a threshold is the bio-based content of the solvent, which must be at least 25%.[36] Additionally, the biomass feedstock must be classified as sustainable, either by formal certification or an equivalent assessment. Finally, any solvent containing ether functionality presents a risk of peroxide formation; as such auto-oxidation potential must be evaluated at an early stage.[37]

Step 7: Assessing solvent application and toxicology

The performance of the candidate solvent must be assessed in applications for which it has been predicted to be useful. When creating replacements for general purpose laboratory solvents, model reactions such as Friedel-Crafts acylation (see later), Menshutkin *N*-alkylation,[14] Diels-Alder cycloadditions,[38] and cross-coupling reactions[39] serve well for the demonstration of polar solvents. Esterification reactions and amidations are suitable for the demonstration of weak and non-hydrogen bonding solvents.[15] Multicomponent reactions forming heterocycles can also be used to test the performance of solvents.[40,41]

Equally important to understand is the toxicity and environmental impact of solvents. However, full toxicity testing is very expensive and time consuming. Quantitative structure-activity relationship (QSAR) methods, such as TEST by the EPA, have gained interest in recent years.[42] QSAR's are statistical models which use a database of chemicals of a known activity, such as median lethal dose (LD_{50}) or bioaccumulation factor (BCF), to predict the unknown activities of other molecules. While predictive software such as TEST is a valuable tool in assessing toxicity, predictions are not always reliable or have a high margin of error. As such, predictions must be confirmed experimentally, which brings us back to the original problem: cost and time. The Ames test is a simple first test of mutagenicity.[43] Although mutagenicity does not imply carcinogenicity, a strong correlation between the two is well established.[43–46] Two mutated *Salmonella typhimurium* (His^-) strains are employed in the Ames test; they are auxotrophic, which means they are unable to synthesize the histidine required for their growth and so cannot survive in the histidine-free media of the Ames test. Mutagenic compounds can revert these His^- strains back to their prototrophic state (His^+), at which point they can synthesise the histidine required for their growth, enabling them to grow in the histidine-free medium. As bacteria cells are different from mammalian cells, rat liver extracts are often used in combination for a more accurate representation of humans. The reason for this that the liver is the organ responsible for the breakdown of ingested material in mammals. Some initially non-mutagenic chemicals can metabolize into mutagens during the breakdown process in the liver.[44,47] Including rat liver extracts in the Ames test increases the likelihood of detecting mutagenic metabolites of a test chemical. The Ames test is a relatively cheap test and test kits can be bought with results obtained in 3 days. Therefore, it is a good starting point for toxicity testing of new molecules. If a substance is found to be mutagenic, it may not be worth committing further time and money into its development. A substance which passes the Ames test would be a good candidate to be taken to the next step of toxicology testing.

Step 8: A techno-economic assessment of the solvent

Techno-economic assessments provide a cost-benefit analysis for the potential manufacture of a solvent, utilising various methods.[48] If the solvent candidate is a suitable product (according to the previous steps) then its commercialisation must be achieved through an environmentally and economically sound process for its benefits to be realised. Techno-economic assessments can be difficult and inaccurate based on lab scale synthetic procedures so it is beneficial to move to several kilograms' scale for a better understanding. Equipment to carry this out is not widely available in university laboratories and so coordination with industrial partners can play a major role in getting new solvents from the lab to commercialisation.

Step 9: Solvent greenness assessed with the CHEM21 solvent selection guide

Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries (CHEM21) is Europe's largest public-private partnership aiming to develop sustainable manufacturing routes to pharmaceuticals. Along with the metrics toolkit,[35] CHEM21 published a solvent selection guide unifying publicly available solvent selections guides from the pharmaceutical industry.[49] The CHEM21 solvent selection guide is easily applied to rank solvents based on proposed criteria of Safety, Health and Environment in compliance with the Global Harmonized System (GHS) and European regulations. This methodology showed good agreement with classical solvents and was also used to rank novel, less classical solvents using a simple and freely available spreadsheet. This same methodology should be used to evaluate the candidate solvent according to the obtained physical and toxicological data.

Step 10: Life cycle assessment (LCA) of the solvent

A life cycle assessment (LCA) is a tool that can be employed to evaluate the environmental impact of a product or process through calculating its emissions. An equivalent tool for the social impact of goods and services, social life cycle assessment (S-LCA), is also possible.[50,51] Before a commitment to manufacturing is made, a pro-active application of LCA is needed to help guide the development of the process. Life cycle assessment can also be applied retrospectively to identify and eliminate areas of concern as they arise.

Results and discussion

In the case study presented, the methodology described above was used to direct the development of a new bio-based solvent. Each step acts a filtering process, whereby any solvent candidates failing to meet the requirements, whether they be enforced by legislation or imposed by user requirements, can be disregarded to focus resources.

Step 1: Identifying halogenated solvents for replacement

As shown in Figure 2, currently there is only one aprotic bio-based solvent (Cygnet 0.0) with a medium to high dipolarity ($0.50 < \pi^* < 1.00$) and a low basicity ($\beta < 0.3$).[52] In this area on a conventional aprotic solvent map reside the halogenated solvents dichloromethane (DCM) and chloroform, which are rated as hazardous and highly hazardous respectively.[49] In addition, suitable physical properties such as boiling point are desired but not priority in this study. The advantage of a higher boiling point is that less solvent is lost to the atmosphere but with the disadvantage of more difficult removal at the end of a process. Therefore, it is important to develop new bio-based solvents which occupy this area of the map. Any solvent with the polarity of halogenated solvents but without the implicit issues surrounding the presence of a halogen atom would be a highly valuable addition to the current catalogue of bio-based solvents.

Step 2: Selecting organic carbonates of glycerol formal and solketal as candidate solvents

Glycerol and its derivatives are well established in the field of bio-based solvent research.[19,53,54] Glycerol is a versatile compound which has many green merits such as being renewable, non-toxic (LD_{50} = 12,600 mg/kg), biodegradable and cheap.[55,56] Glycerol is a by-product of biodiesel production through the transesterification of triglycerides and was listed by the National Renewable Energy Laboratory (NREL) as one of the top twelve platform molecules which can be derived from biomass.[57] Approximately 10 kg of crude glycerol can be obtained during the production of 100 kg of biodiesel. Due to the large volumes of glycerol produced, biological or chemical conversion of surplus glycerol to high-value products has received significant attention.[58]

At present, the main research fields of glycerol derived solvents are alkyl glycerol ethers, glycerol carbonate/esters of glycerol carbonate, glycerol-based ILs, glycerol formal and solketal.[59] The modification of glycerol formal and solketal (solvents in their own right) into new aprotic solvents is an unexploited field. Reacting at the alcohol can produce aprotic molecules, and the extended functionality may well increase dipolarity without increasing the hydrogen bond basicity (β). The organic carbonates of glycerol formal and solketal were identified as the target molecules in this work (Scheme 1).

Step 3: *In silico* modelling to identify the target solvent

Potential new carbonate solvents, produced from glycerol formal and solketal, and their properties are listed in Table 1. The Hansen solubility parameters of DCM and chloroform were selected as references. The boiling point and R_a (relative to DCM and chloroform) of each candidate was calculated in HSPiP. After the screening, methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC) was selected as the target solvent due to its lower R_a to DCM and chloroform. The predicted boiling point of MMC (222 °C) is much higher than that of DCM or chloroform but this is unavoidable given the molecular size and structure. However, the similar solvency power of MMC to these halogenated solvents could remain interesting. The position of MMC and other nearby conventional solvents in the 3D Hansen space can be seen in the electronic supplementary information (ESI S1).

Table 1. HSPiP predicted properties of candidate bio-based carbonate solvents synthesised from glycerol derivatives.

Potential bio-based solvents	B.P./°C	Hansen δ_D/MPa$^{0.5}$	Hansen δ_P/MPa$^{0.5}$	Hansen δ_H/MPa$^{0.5}$	R_a to DCM[a]	R_a to chloroform[a]
1	206	17.0	10.3	8.1	5.08	7.76
2	211	17.0	10.1	8.1	4.92	7.57
3 (MMC)	222	16.2	7.9	6.0	4.31	5.78
Chloroform	61	17.8	3.1	5.7	-	-
DCM	40	17	7.3	7.1	-	-

Step 4: Selecting the greenest synthetic pathway to MMC from solketal

As shown in Scheme 2, there are two main methods by which to synthesise MMC from solketal, carboxymethylation via methyl chloroformate (MC) (i) or DMC (ii). Metrics analysis applying the Chem21 toolkit using conditions taken from model reactions found in the literature are displayed in table 2.[60,61] As is evident, yields and atom economy and PMI for either route are very similar. RME is significantly worse for route (ii) as DMC acts as both a reactant and solvent, but is an acceptable solvent as opposed to acetonitrile which is problematic. The most significant difference is in the inherent health and safety, with dimethyl carbonate widely accepted as a biodegradable and non-toxic green compound,[62] as opposed to methyl chloroformate which is highly toxic. Thus, the DMC synthesis is more promising as a green route to MMC.

Table 2. Analysis of route (i) and (ii) by the Chem21 metrics toolkit.

Pathway	(i)	(ii)
Yield	85%	90%
Rxn. Mass Efficiency	59%	9%
Atom Economy	84%	86%
Solvents	acetonitrile	dimethyl carbonate
Health & Safety	H330 (methyl chloroformate)	
Mass intensity	15	12
Catalysts used	Indium	Stoichiometric reagent
Reactor	Batch	Batch
Elements	Indium	Potassium
Energy	Room temperature	Reflux
Workup	Quench, distil	Distil

Step 5: MMC synthesis and optimisation

Although MMC synthesised from solketal *via* DMC chemistry has been previously reported,[21] conditions were applied to preferentially give methylation as opposed to carboxymethylation. Additionally, the products were synthesised as part of a mechanistic study and not considered as solvents. As such optimisation towards carboxymethylation and determination of further physical properties were required. In this work, MMC was synthesised and the procedure was optimised (see ESI). The optimised reaction conditions are: reaction time = 20 h, 0.1 mol% K_2CO_3 and DMC/solketal mole ratio = 20:1. The isolated yield of MMC after distillation was 91% (99% purity by GC).

Step 6: Determining MMC's physical properties and tendency towards peroxide formation

Table 3 lists the experimentally observed properties of MMC. The boiling point of MMC was measured to be 232 °C by distillation, only 10 °C higher than the HSPIP estimate. Distillation is extensively used as a product isolation technique in batch processes and therefore solvents with high boiling points, such as MMC, can be problematic unless the product can be crystalized from solution with relative ease. The melting point was determined to be -7 °C by differential scanning calorimetry (DSC), potentially limiting MMC's use in low temperature chemistry. The density of MMC was determined to be 1.14 g·cm^{-3} at 298 K, similar to DCM and chloroform. The viscosity of MMC is also comparatively high as compared to other solvents which may generate issues in processing.

Like many other bio-based solvents, MMC does not contain any halogen atoms or heteroatoms aside from oxygen, thus eliminating environmental risk to the ozone layer and atmospheric pollution in the form of NO_x and SO_x. Methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate is immiscible with water, enabling applications in liquid-liquid extractions, although more testing is needed in this regard.

As MMC contains ether functionality, it has the potential to produce explosive peroxide compounds *via* autoxidation by atmospheric O_2. An initial test to investigate the formation of peroxides in MMC was carried out by employing peroxide test strips (Macherey-Nagel, QUANTOFIX® Peroxide-100) to test for

Table 3. The properties of MMC compared to DCM and chloroform.

Properties	MMC	DCM	Chloroform
MWt	190.2[a]	84.9[15a]	119.4[15a]
α	0.00	0.13[15b]	0.20[15b]
β	0.29	0.10[15b]	0.10[15b]
π^*	0.67	0.82[15b]	0.58[15b]
δ_D/MPa$^{0.5}$	16.2[a]	18.2[15c]	17.8[15c]
δ_P/MPa$^{0.5}$	7.9[a]	6.3[15c]	3.1[15c]
δ_H/MPa$^{0.5}$	6.0[a]	6.1[15c]	5.7[15c]
HSP distance[b]	0.0	4.3	5.8
B.P. /°C	232[c]	40[15a]	61[15a]
M.P. /°C	-7[d]	-95[15a]	-64[15a]
ρ /g·cm^{-3} 298 K	1.14	1.32[15a]	1.48[15a]
Viscosity /cP 293 K	3.50	0.44[15d]	0.58[15f]

any peroxides present in solution. After 224 days of testing without antioxidants or stabilisers, peroxide concentration in MMC was below the detection limit. This demonstrates MMC did not readily form peroxides at ambient temperatures over the period of testing, although the routine addition of a stabiliser is recommended.

Its position on the solvent map indicates that MMC has similar solubility properties to dimethyl carbonate, 1,4-dioxane, acetonitrile and acetic anhydride (Figure 2). These results are evidence that MMC too readily accepts hydrogen-bonds to be considered a replacement for the halogenated solvents DCM and chloroform. Moreover, since MMC is like DMC in terms of polarity, it may not be beneficial to consume DMC to make MMC. However, MMC fulfils the criteria to undergo performance and toxicological testing.

Step 7: Assessing the performance of MMC as a solvent and toxicological testing

Friedel-Crafts acylation and Diels-Alder cycloaddition reactions were selected to evaluate the performance of MMC compared to traditional solvents. If, by chance, the performance of MCC exceeded the expectations established by its measured polarity, it would be worth pursuing beyond this stage of solvent development. These two reactions are commonly performed with halogenated solvents. Analysis of the experimental results allows a comparison of the solvent performance of MMC with a range of traditional solvents. The synthesis of 4-methoxyacetophenone (4-MAP) from anisole and acetic anhydride catalysed by $FeCl_3$ (Scheme 3, (iii)) was selected to evaluate the performance of MMC in the Friedel-Crafts reaction. It was found that the reaction conducted in MMC resulted in a yield of 61% 4-MAP (Figure 3). Although this is lower than when using DCM, it is higher than all other solvents tested.

The performance of MMC was also assessed in the synthesis of 1-(3,4-dimethylcyclohex-3-enyl) ethanone (DE) from 2,3-dimethylbuta-1,3-diene (diene) and 3-buten-2-one, catalysed by anhydrous $YbCl_3$ (Scheme 3, (iv)).[63] Dichloromethane, propylene carbonate and acetonitrile all exhibited high yields (>95%), while ethyl acetate, acetone and MMC produced yields of 75%-80% (Figure 3). These results indicate that the solvent properties of MMC are more similar to ketone and ester solvents in the Diels-Alder reaction.

The results of the two experimental case studies show both reactions are highly dependent on the polarity of the solvent. Specifically, a high π^* is favoured, a trend that is especially true in the case of the Diels-Alder reaction. MMC is competitive in terms of yield, but the superior polarity of DCM makes it the technically more proficient solvent, albeit suspected as a carcinogen. Across both case studies propylene carbonate, with its strong molecular dipole moment, was also apt as a reaction solvent and worth considering as a solvent for these transformations.

The mutagenicity of MMC was tested using the Ames test. TA98 and TA100 were utilised for the detection of frameshift mutations and base substitution mutations, respectively. Dimethyl sulfoxide (DMSO) was employed as a solvent. A mixture of 2-nitrofluorene (2-NF) and 4-nitroquinoline-*N*-oxide (4-NQO) was utilised as the positive control. This Ames test was conducted without S9 microsomal activation and so metabolites could not be investigated. MMC was not found to be mutagenic using the TA100 strain (ESI S3). However, MMC was found to be mutagenic for the TA98 strain (ESI S3). This indicated that MMC is likely to be a mutagenic solvent and hence, a possible carcinogen. Consequently, although MMC is a bio-based solvent, its potential toxicity means it is unlikely to be considered for further testing for use as a green solvent. This assay demonstrates the usefulness of the Ames test as a first port of call for toxicity testing and that any new bio-based solvent needs toxicological test before application. The remaining 3 steps have not been completed for MMC as the solvent failed to pass step 7, however were techno economic assessment included, many detailed examples in the literature could have been emulated.

Step 8: A techno-economic assessment of the solvent

Specific examples regarding solvents can be found in the comparison of various small alcohols from biomass,[64] different strategies towards ethanol bio-refineries,[65] and strategies towards production of various fatty esters.[66] The majority of such studies have so far been directed towards fuels where margins are very tight but for a new bulk chemical to be industrially feasible it must meet the triple bottom line, to have an environmental, social and economic advantage.[67] As such, any new bio-based solvent must demonstrate a theoretical economic competitiveness to be further considered. A key factor that is missing from the principles of green chemistry is that any green product or synthesis must be cost effective. It is therefore of vital importance to undertake a techno-economic assessment of the solvent. If at this stage MMC was found to be cost competitive and feasible, further Safety, Health and Environment testing would be required in step 9.

Step 9: Solvent greenness assessed with the CHEM21 solvent selection guide

As stated, this is a simple assessment criteria to apply using the published methodology. The data collected in step 6 is sufficient to gain an accurate safety score, with the exception of resistivity which requires specialised equipment to determine as the high impedance requires a high voltage to be applied. With reference to the health and environment ranking, as MMC is relatively novel, it has no Global Harmonized System (GHS) hazard statements nor is it REACH registered which would result in a default score of 5 (problematic) in both categories. Testing required to generate GHS data and meet REACH criteria is potentially expensive and laborious and thus should only be carried out on solvents of real promise. If MMC was still a promising candidate at this stage the full green credentials would be assessed and then the molecule would be registered under REACH, thus providing the comprehensive physical properties, toxicological data and environmental data for the solvent. However, the mutanagenic results associated with MMC would make it a

potential Substance of Very High Concern, requiring the full annex VIII data set.[68]

Step 10: Life cycle assessment (LCA) of the solvent

At the same time as REACH registration is being sought, a full cradle to grave LCA of the solvent will provide a holistic assessment of the solvent. Thus providing investors and end users with the confidence to commercialise the process or utilise the solvent in their processes.

Conclusion

In this work, a methodology to focus the development of new bio-based solvents was proposed in order to accelerate the implementation of greener solvents. A case study on the development of a potential bio-based solvent, methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC), was carried out to exemplify the process. Although MMC is an attractive candidate as a replacement solvent, simply being bio-derived is not enough for a molecule to be regarded as green. This work highlights a systematic method for the development of bio-based solvents, which importantly promotes the use of toxicity testing at an early stage in the development of bio-based molecules. The Hansen solubility parameters and reaction data indicated that MMC could be an attractive bio-based aprotic solvent. The KAT parameters of MMC clarified its polarity, potential reactivity and were found to be similar to dimethyl carbonate. More importantly, MMC was found to be a mutagen in a preliminary Ames tests. The methodology of bio-based solvent development described here is a widely applicable approach that highlights the significance of using KAT parameters and toxicology research in the early stage of exploitation of any new bio-based solvent. The combination of such a protocol and the utilisation of the European technical specification (CEN/TS 16766:2015) for bio-based solvents can be an efficient way forward for the rational substitution of hazardous, unsustainable solvents.

Acknowledgements

The authors work like to thank the Biorenewables Development Centre (BDC) for their assistance with the Ames test. The authors also thank Dr. Thomas J. Farmer for his beneficial suggestions during this research.

Notes and references

1 C. Reichardt and T. Welton, *Solvents and Solvent Effects in Organic Chemistry*, John Wiley & Sons, 2011.
2 F. M. Kerton and R. Marriott, *Alternative Solvents for Green Chemistry*, Royal Society of Chemistry, 2013.
3 *Global Solvents-Opportunities for Greener Solvents. Available online at https://www.ihs.com/products/chemical-special-reports-global-solvents.html, (accessed September 2016).*
4 M. J. Molina and F. S. Rowland, *Nature*, 1974, **249**, 810–812.
5 P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2009, **39**, 301–312.
6 European REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
7 Candidate List of substances of very high concern for Authorisation. Available online at http://echa.europa.eu/web/guest/candidate-list-table (accessed June 2016).
8 Substances restricted under REACH. Available online at http://echa.europa.eu/addressing-chemicals-of-concern/restrictions/substances-restricted-under-reach (accessed June 2016).
9 European Commission Rapid Alert System for dangerous non-food products (RAPEX). Available online at http://ec.europa.eu/consumers/consumers_safety/safety_products/rapex/index_en.htm, (accessed December 2016).
10 Canadian Environmental Protection Act, 1999. Available online at http://laws-lois.justice.gc.ca/eng/acts/c-15.31/page-1.html, (accessed September 2016).
11 US EPA, Code of Federal Regulations (CFR) CFR Title 40. Available online at, http://www.archives.gov/federal-register/cfr/subject-title- 40.html, (accessed September 2016).
12 Y. Gu and F. Jérôme, *Chem. Soc. Rev.*, 2013 **12**, 1127-1138.
13 J. H. Clark, T. J. Farmer, A. J. Hunt and J. Sherwood, *Int. J. Mol. Sci.*, 2015, **16**, 17101–17159.
14 J. Sherwood, M. D. Bruyn, A. Constantinou, L. Moity, C. R. McElroy, T. J. Farmer, T. Duncan, W. Raverty, A. J. Hunt and J. H. Clark, *Chem. Commun.*, 2014, **50**, 9650–9652.
15 J. H. Clark, D. J. Macquarrie and J. Sherwood, *Green Chem.*, 2012, **14**, 90–93.
16 D. F. Aycock, *Org. Process Res. Dev.*, 2006, **11**, 156–159.
17 P. S. Kulkarni, C. Brazinha, C. A. M. Afonso and J. G. Crespo, *Green Chem.*, 2010, **12**, 1990–1994.
18 C. S. M. Pereira, V. M. T. M. Silva and A. E. Rodrigues, *Green Chem.*, 2011, **13**, 2658–2671.
19 Y. Gu and F. Jérôme, *Chem. Soc. Rev.*, 2013, **42**, 9550–9570.
20 European standard CEN/TS 16766, Bio-based Solvents - Requirements and Test Methods, European Committee for Standardization (CEN), Brussels, 2015.
21 M. Selva, V. Benedet and M. Fabris, *Green Chem.*, 2012, **14**, 188–200.
22 R. W. Taft and M. J. Kamlet, *J. Am. Chem. Soc.*, 1976, **98**, 2886–2894.
23 M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 377–383.
24 M. J. Kamlet, J. L. Abboud and R. W. Taft, *J. Am. Chem. Soc.*, 1977, **99**, 6027–6038.
25 P. G. Jessop, D. A. Jessop, D. Fu and L. Phan, *Green Chem.*, 2012, **14**, 1245–1259.
26 R. Gani, C. Jiménez-González and D. J. C. Constable, *Comput. Chem. Eng.*, 2005, **29**, 1661–1676.
27 R. Gani, *Chem. Eng. Res. Des.*, 2004, **82**, 1494–1504.
28 R. Gani, P. A. Gómez, M. Folić, C. Jiménez-González and D. J. C. Constable, *Comput. Chem. Eng.*, 2008, **32**, 2420–2444.
29 L. Moity, V. Molinier, A. Benazzouz, R. Barone, P. Marion and J.-M. Aubry, *Green Chem.*, 2014, **16**, 146-160.
30 L. Moity, V. Molinier, A. Benazzouz, B. Joossen, V. Gerbaud and J.-M. Aubry, *Green Chem.*, 2016, **18**, 3239–3249.
31 C. M. Hansen, PhD thesis, Technical University of Denmark, 1967.
32 C. M. Hansen, *Hansen Solubility Parameters: A User's Handbook, Second Edition*, CRC Press, 2012.
33 S. A. and C. M. Hansen, Hansen Solubility Parameters in Practice (HSPiP 4.1.04), Hansen-Solubility, 2008.
34 T. Farmer and M. Mascal, in *Introduction to Chemicals from Biomass,* ed. J. Clark, F. Deswarte, John Wiley & sons, Ltd., Chichester, 2nd edn, 2015, ch. 4.

35 C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111-3121.
36 J. Sherwood, J. H. Clark, T. J. Farmer, L. Herrero-Davila and L. Moity, *Molecules*, 2016, **22**, 48.
37 V. Fábos, G. Koczó, H. Mehdi, L. Boda and I. T. Horváth, *Energy Environ. Sci.*, 2009, **2**, 767.
38 R. Bini, C. Chiappe, V. L. Mestre, C. S. Pomelli and T. Welton, *Org. Biomol. Chem.*, 2008, **6**, 2522–2529.
39 H. L. Parker, J. Sherwood, A. J. Hunt and J. H. Clark, *ACS Sustain. Chem. Eng.*, 2014, **2**, 1739–1742.
40 J. Sherwood, H. L. Parker, K. Moonen, T. J. Farmer and A. J. Hunt, *Green Chem.*, 2016, **18**, 3990-3996.
41 J. H. Clark, D. J. Macquarrie and J. Sherwood, *Chem. – Eur. J.*, 2013, **19**, 5174–5182.
42 Toxicity Estimation Software Tool (TEST). Available online at https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test (Accessed January 2017).
43 B. N. Ames, F. D. Lee and W. E. Durston, *Proc. Natl. Acad. Sci.*, 1973, **70**, 782–786.
44 A. J. Griffiths, J. H. Miller, D. T. Suzuki, R. C. Lewontin and W. M. Gelbart, in *An Introduction to Genetic Analysis,* W.H. Freedman, New York, 7th edn, 2000, ch. 16.
45 J. McCann, L. Swirsky Gold, L. Horn, R. McGill, T. E. Graedel and J. Kaldor, *Mutat. Res. Toxicol.*, 1988, **205**, 183–195.
46 J. McCann, E. Choi, E. Yamasaki and B. N. Ames, *Proc. Natl. Acad. Sci.*, 1975, **72**, 5135–5139.
47 B. N. Ames, W. E. Durston, E. Yamasaki and F. D. Lee, *Proc. Natl. Acad. Sci.*, 1973, **70**, 2281–2285.
48 C. L. Gargalo, A. Carvalho, K. V. Gernaey and G. Sin, *Biochem. Eng. J.*, 2016, **116**, 146–156.
49 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2015, **18**, 288–296.
50 A. Jørgensen, A. L. Bocq, L. Nazarkina and M. Hauschild, *Int. J. Life Cycle Assess.*, 2008, **13**, 96.
51 C. Benoît, G. A. Norris, S. Valdivia, A. Ciroth, A. Moberg, U. Bos, S. Prakash, C. Ugaya and T. Beck, *Int. J. Life Cycle Assess.*, 2010, **15**, 156–163.
52 A. Alves Costa Pacheco, J. Sherwood, A. Zhenova, C. R. McElroy, A. J. Hunt, H. L. Parker, T. J. Farmer, A. Constantinou, M. De bruyn, A. C. Whitwood, W. Raverty and J. H. Clark, *ChemSusChem*, 2016, **9**, 3503–3512.
53 A. Wolfson, A. Snezhko, T. Meyouhas and D. Tavor, *Green Chem. Lett. Rev.*, 2012, **5**, 7–12.
54 G. Cravotto, L. Orio, E. C. Gaudino, K. Martina, D. Tavor and A. Wolfson, *ChemSusChem*, 2011, **4**, 1130–1134.
55 R. Ciriminna, C. D. Pina, M. Rossi and M. Pagliaro, *Eur. J. Lipid Sci. Technol.*, 2014, **116**, 1432–1439.
56 Z. Wang, J. Zhuge, H. Fang and B. A. Prior, *Biotechnol. Adv.*, 2001, **19**, 201–223.
57 J. J. Bozell and G. R. Petersen, *Green Chem.*, 2010, **12**, 539–554.
58 Biofuels Barometer 2016. Available online at http://www.eurobserv-er.org/pdf/biofuels-barometer-2016-en/ (accessed August 2016).
59 A. E. Díaz-Álvarez, J. Francos, B. Lastra-Barreira, P. Crochet and V. Cadierno, *Chem. Commun.*, 2011, **47**, 6208–6227.
60 J.-G. Kim and D. O. Jang, *Tetrahedron Lett.*, 2009, **50**, 2688–2692.
61 P. Tundo, F. Aricò, A. E. Rosamilia, M. Rigo, A. Maranzana and G. Tonachini, *Pure Appl. Chem.*, 2009, **81**, 1971–1979.
62 M. Bilde, T. E. Møgelberg, J. Sehested, O. J. Nielsen, T. J. Wallington, M. D. Hurley, S. M. Japar, M. Dill, V. L. Orkin, T. J. Buckley, R. E. Huie and M. J. Kurylo, *J. Phys. Chem. A*, 1997, **101**, 3514–3525.
63 X. Fang, B. P. Warner and J. G. Watkin, *Synth. Commun.*, 2000, **30**, 2669–2676.
64 L. Tao, E. C. D. Tan, R. McCormick, M. Zhang, A. Aden, X. He and B. T. Zigler, *Biofuels, Bioprod. Bioref.*, 2014, **8**, 30-48.
65 D. Klein-Marcuschamer, B. A. Simmons and H. W. Blanch, *Biofuels, Bioprod. Bioref.*, 2011, **5**, 562-569.
66 L. Amer, B. Adhikari and J. Pellegrino, *Bioresorce Technol.* 2011, **102**, 9350-9359.
67 B. Willard, The new sustainability advantage: seven business case benefits of a triple bottom line, New Society Publishers, 2012.
68 ECHA Information requirements. Available online at https://echa.europa.eu/regulations/reach/registration/information-requirements (Accessed January 2017).