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2,2,5,5-Tetramethyltetrahydrofuran (TMTHF): a non-polar, non-peroxide forming ether replacement for hazardous hydrocarbon solvents†

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An inherently non-peroxide forming ether solvent, 2,2,5,5-tetramethyltetrahydrofuran (2,2,5,5-tetramethyloxolane), has been synthesized from readily available and potentially renewable feedstocks, and its solvation properties have been tested. Unlike traditional ethers, its absence of a proton at the alpha-position to the oxygen of the ether eliminates the potential to form hazardous peroxides. Additionally, this unusual structure leads to lower basicity compared with many traditional ethers, due to the concealment of the ethereal oxygen by four bulky methyl groups at the alpha-position. As such, this molecule exhibits similar solvent properties to common hydrocarbon solvents, particularly toluene. Its solvent properties have been proved by testing its performance in Fischer esterification, amidation and Grignard reactions. TMTHF's differences from traditional ethers is further demonstrated by its ability to produce high molecular weight radical-initiated polymers for use as pressure-sensitive adhesives.

Introduction

The volatile, non-polar (VNP) class of solvent is important and widely used, with applications as reaction media in synthetic chemistry, in liquid–liquid extractions and in the coating industry where rapid removal by evaporation is necessary. However, many VNP solvents such as the hydrocarbons hexane and toluene have been recognized as hazardous air pollutants by the US EPA[1] and both are suspected of damaging fertility as defined under REACH.[2,3] Furthermore, hexane is currently on a CoRAP list for evaluation due to carcinogenicity, mutagenicity and reprotoxicity (CMR) concerns.[4] VNP solvents have been targeted for replacement with safer, non-volatile, and ideally renewable alternatives in many recent reviews and solvent guides,[5–7] but this has proven to be difficult. Although many traditionally used VNP solvents can be made from biomass,[8,9] the same toxicity and flammability issues as their petroleum-based equivalents persist.[2,10]

Many of the candidates to replace VNP solvents have much higher boiling points than the solvent to be replaced. While limonene and *para*-cymene have similar solvent properties to toluene, product isolation by solvent removal is challenging and energy intensive due to their high boiling points, 176 and 177 °C respectively.[11] Unless a product can be easily crystallized from the reaction medium, solvent removal by evaporation is often the only alternative. Volatility is a solvent property which can improve the greenness of a process by facilitating recovery.[12] The energy demand to remove less-volatile solvents such as limonene and *para*-cymene, can impair the environmental credentials of an otherwise green process. Until new processes and products have been developed which do not require solvent evaporation, green, volatile, and safe solvents are needed.

Esters are another attractive alternative as they generally do not possess the high toxicity of hydrocarbons which is demonstrated by their natural presence in foods and use as flavour additives.[13] However, at low molecular weights, esters have higher polarity compared to hydrocarbon solvents, impeding their use as VNPs.[14] At higher molecular weights the polarity of esters decreases but with the consequence that their boiling point increases, making product isolation by solvent evaporation energy intensive.[15]

Many supposedly greener ethers such as cyclopentyl methyl ether (CPME), 2-methyltetrahydrofuran (2-MeTHF) and 2,5-dimethyltetrahydrofuran (DMTHF) have a suitable balance of polarity and volatility to replace traditional VNP solvents, but safety issues persist due to their explosive peroxide-forming potential, questioning their green credentials.[16–18] Improved safety has been claimed in the case of CPME but an antioxidant additive, butylated hydroxytoluene (BHT), is required to prevent peroxidation.[16,19] Issues regarding the peroxide

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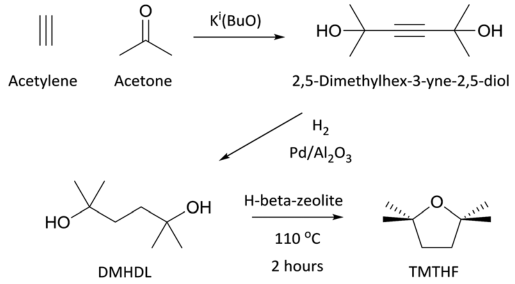


Fig. 1 Synthetic route to TMTHF.

forming potential of ethers has recently been reflected in the pharmaceutical industry CHEM21 solvent selection guide where 2-MeTHF and CPME are classed as problematic, while DMTHF has not yet been classified.[6]

Thus, there is a real need to develop a safer VNP solvent, evidenced by limited peroxide formation and low mutagenicity. Additionally, boundaries were set for a solvent with a boiling point <115 °C (comparable to toluene), a melting point <−15 °C (for storage in cold climates) and an ability to dissolve polyisoprene rubber (as a verification of non-polarity). Herein, the facile synthesis (Fig. 1) and testing of the non-peroxide forming (without the use of anti-oxidant additives) ether, 2,2,5,5-tetramethyltetrahydrofuran (TMTHF, IUPAC = 2,2,5,5-tetramethyloxolane), has been described. It was demonstrated to be a safer, potentially renewable alternative to traditional VNP solvents. TMTHF's resistance to peroxide formation has been investigated and compared to current commercially available ether solvents. Finally, its viability as a replacement for VNP solvents has been demonstrated by its application in a series of synthetic reactions, radical-initiated polymerizations and solubility tests, and finally its green credentials are discussed.

Results and discussion

Synthesis of TMTHF

TMTHF was prepared *via* the facile dehydration of readily available 2,5-dimethylhexane-2,5-diol (DMHDL). A moderate temperature of 110 °C in the presence of a suitable heterogeneous solid acid catalyst was found to be sufficient for the synthesis of TMTHF. A catalyst screen of a range of solid acid catalysts showed that H-beta-zeolites fully convert DMHDL with excellent selectivity of >99% for TMTHF (Fig. S1, ESI†) at low catalyst loadings.[20] At 1 wt% catalyst loading, a reaction time of 2 hours was sufficient for full conversion of DMHDL. Silica/alumina ratios of 25 : 1 and 150 : 1 were tested with no variation in yield observed between them (Fig. S1, ESI†). Other solid acid catalysts were also found to produce TMTHF in good yields (Fig. S1, ESI†), but were discounted as a result of noticeable side-product formation (**1**, **2**, **3**, **4**, Fig. S2, ESI†).

The high yielding beta-zeolite catalysed synthesis was easily scaled to 1 L, using a reactive distillation apparatus (Fig. S3, ESI†) which simultaneously purified TMTHF by removing small amounts of higher boiling point side-products. This flow-type apparatus allowed the continuous production of TMTHF by simply adding more DMHDL. Multiple reuse of the zeolite catalyst was possible by filtering from the reaction residue and calcining at 600 °C for 4 hours, resulting in no noticeable loss of catalyst performance in 500 g scale (w.r.t. DMHDL) batches over a six-month period. Fig. S1 (ESI†) shows yields from three successive reactions using the same catalyst, although many more were subsequently carried out with similarly high performance.

The starting material, DMHDL, is currently produced on a large scale from the reaction of acetylene and acetone *via* 2,5-dimethylhex-3-yne-2,5-diol for use in polyethylene copolymers.[21,22] The only by-products in the production of TMTHF are potassium phosphate from the coupling of acetylene and acetone, and water from the ring closure of DMHDL. Potassium phosphate has significant potential for downstream use as a fertilizer in agricultural applications. This results in a highly efficient production process (atom economy (AE) = 96%, reaction mass efficiency (RME) = 93%). Using bio-based drop-in acetone and acetylene as the starting materials, renewable TMTHF can be produced, securing its long term production and sustainability (see ESI† for proposed synthetic routes).[23–26]

Peroxide tests

Autoxidation to form peroxides is known to occur readily in many chemical compounds, and is particularly an issue with ethers.[27–31] The subsequently formed low-molecular weight peroxides are extremely unstable compounds and in many cases are shock sensitive.[27] While the rates of peroxide formation in some chemical classes in certain conditions have been reported, little is known about the concentrations at which they become explosive.[27,32]

As such, standardized methods of measurement have not been established and safety thresholds are vaguely defined as 100 ppm.[27,32] Peroxide formation in ethers occurs when protons on the alpha-carbon to the ethereal oxygen are abstracted by low energy visible light or by a radical initiator [eqn (1)], followed by oxidation by atmospheric oxygen to form a radical (R–O–O$^•$) [eqn (2)]. Propagation continues when a newly formed radical abstracts an alpha-proton from an adjacent ether molecule, producing a hydroperoxide (R–O–O–H) and another ether radical (R$^•$) [eqn (3)].[28]

$$\mathrm{RH} \xrightarrow{h\nu} \mathrm{R}^{\bullet} + \mathrm{H}^{\bullet} \tag{1}$$

$$\mathrm{R}^{\bullet} + \mathrm{O_2} \rightarrow \mathrm{ROO}^{\bullet} \tag{2}$$

$$\mathrm{ROO}^{\bullet} + \mathrm{RH} \rightarrow \mathrm{ROOH} + \mathrm{R}^{\bullet} \tag{3}$$

Replacing the adjacent alpha-protons with stronger bonding groups, such as methyl groups, limits the peroxide forming potential of the ether molecule *via* the aforementioned mechanism.

This is demonstrated by 1,8-cineol (eucalyptol), a naturally occurring monoterpenoid ether which contains two quaternary

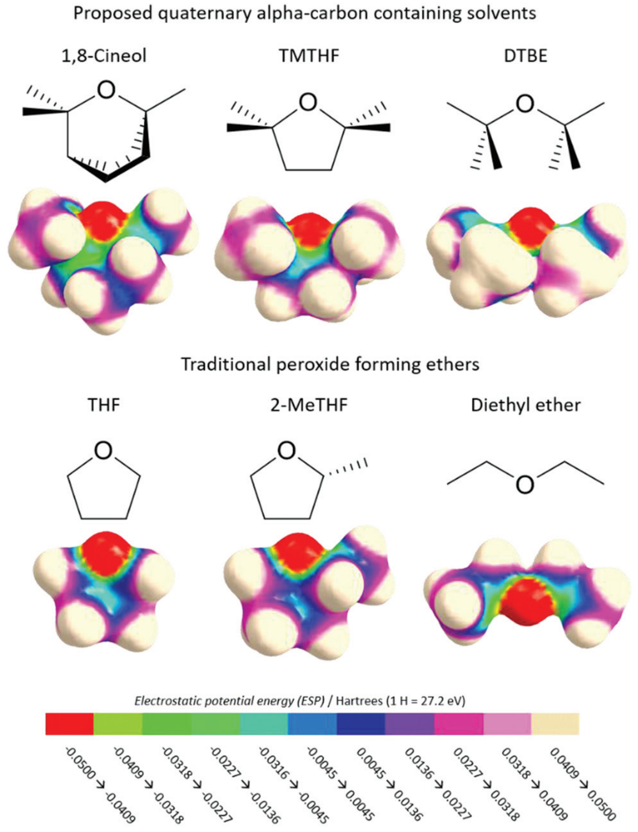


Fig. 2 Argus labs picture of quaternary and traditional ethers.

carbons at both alpha-positions to its ethereal oxygen (Fig. 2). 1,8-Cineol has previously been shown not to form hydroperoxides upon oxidation but instead breaks down innocuously into ketones, acids and aldehydes.[33] It can be utilized as a solvent, but its high boiling point (176–177 °C) prevents its use in applications where high volatility is essential. Many similarly inherently non-peroxide forming ether structures which contain two quaternary alpha-carbons can be designed but only two structures, 2,2,5,5-tetramethyltetrahydrofuran (TMTHF) and di-*tert*-butyl ether (DTBE), boast solubility properties and a boiling point within the limits set in this work (Fig. 2 and Table 1). Adding further functionality to either of these molecules increases their boiling points above the threshold set, making further derivatives unsuitable for many standard applications of VNP solvents. Although both candidates look promising as non-peroxide forming ethers, DTBE cannot be synthesized by the obvious acid catalysed route using *tert*-butanol and isobutene.[34,35] Alternative routes produce by-products resulting in low atom economies, making the use of DTBE as a solvent less attractive and as such, it was not considered further in this work.[34,36–38]

As already demonstrated, TMTHF can be produced catalytically from readily accessible cheap and bio-available molecules (acetylene and acetone) *via* an atom economic pathway. Its resistance to peroxide formation has been shown experimentally in comparison to other common ethers, in conditions which accelerate the rate of peroxide formation. Air was bubbled through TMTHF, CPME, 2-MeTHF, THF with irradiation by UV light (254 nm) in the absence of antioxidants. Peroxide formation was observed in varying amounts in CPME, 2-MeTHF and THF upon irradiation for 3 hours (Table S1, ESI†). In contrast, TMTHF did not form any detectable peroxides in the same conditions. When TMTHF was placed under the even harsher conditions of bubbling air, UV irradiation while under reflux, still no peroxide formation was observed. Furthermore, the concentration of peroxides in CPME, 2-MeTHF and THF increased over 6 months under normal storage conditions (brown chemical bottles with septum seal) whereas TMTHF did not form any detectable peroxides in the same time scale.

Table 1 The physical properties of TMTHF shown in comparison to a range of hydrocarbon, traditional ether and other quaternary ether solvents

	Hydrocarbons			Quaternary ethers			Traditional ethers		
Solvent property	Hexane	C-Hexane	Toluene	1,8-Cineol	TMTHF	DTBE	THF	2-MeTHF	Diethyl ether
M_w/g mol^{-1}	86.18	84.16	92.14	154.25	128.25	130.23	72.11	86.13	74.12
Boiling point/°C	69[a]	81[a]	111[a]	176[a]	112[b]	107[c]	66[a]	78[d]	35[a]
Melting point/°C	−95[a]	6[a]	−95[a]	2[a]	<−90[b]	<−90[b]	−108[a]	−136[d]	−116[a]
Density/g ml^{-1}	0.661[a]	0.778[a]	0.867[a]	0.927[a]	0.802[b]	0.762[c]	0.883[a]	0.854[d]	0.713[a]
Mol. vol./cm^{-3} mol^{-1}	131.4[e]	108.9[e]	106.6[e]	167.5[e]	151.1[e]	172.5[e]	81.9[e]	100.2[e]	104.7[e]
AIT/°C	225[a]	245[a]	522[f]	No data	417[f]	No data	321[a]	270[g]	180[a]
LEL/v/v%	1.1[a]	1.3[a]	1.1[h]	No data	0.9[h]	No data	2.0[a]	1.5[g]	1.9[a]
δ_D/MPa$^{0.5}$	14.9[e]	16.6[e]	18.0[e]	16.6[e]	15.4[e]	14.0[e]	16.8[e]	16.9[e]	14.5[e]
δ_P/MPa$^{0.5}$	0[e]	0[e]	1.4[e]	2.5[e]	2.4[e]	2.5[e]	5.7[e]	5.0[e]	2.9[e]
δ_H/MPa$^{0.5}$	0[e]	0[e]	2.0[e]	2.5[e]	2.1[e]	1.4[e]	8.0[e]	4.3[e]	5.4[e]
δ/MPa$^{0.5}$	14.9[e]	16.6[e]	18.2[e]	16.9[e]	15.7[e]	14.3[e]	19.5[e]	18.1[e]	15.0[e]
A	0.00[i]	0.00[i]	0.00[i]	0.00[i]	0.00[i]	0.00[i]	0.00[i]	0.00[i]	0.00[i]
B	0.00[j]	0.00[j]	0.10[j]	0.72[j]	0.77[j]	0.51[j]	0.58[j]	0.58[l]	0.47[m]
π^*	0.00[k]	0.00[k]	0.51[k]	0.41[k]	0.35[k]	0.17[k]	0.59[k]	0.53[l]	0.27[m]
$\log P_{(o/w)}$	4.00[n]	3.44[n]	2.73[n]	2.28[b]	1.92[b]	2.57[b]	0.46[n]	0.77[b]	0.89[n]

[a] Pubchem. [b] This work. [c] Smutny *et al.*[35] [d] Aycock *et al.*[17] [e] Predicted by HSPiP. [f] Carried out by ITS testing services. [g] Pennakem MSDS.[56] [h] Carried out by Chilworth Technology. [i] Assumed value. [j] This work, using *N*,*N*-diethyl-4-nitroaniline and 4-nitroaniline dyes. [k] This work, using *N*,*N*-diethyl-4-nitroaniline dye. [l] Jessop *et al.*[41] [m] Kamlet *et al.*[39] [n] Sangster.[57]

Physical properties of TMTHF

The physical properties of TMTHF are shown in Table 1. Its boiling point (112 °C) has been determined experimentally and was found to be very close to that of toluene (111 °C). Such a similar boiling point would help ease the substitution from toluene to TMTHF in industrial processes such as in the coating industry, where the boiling point of the coating solvent is a vital consideration. TMTHF's density has been measured experimentally at 293 K to be 0.802 g mL^{-1}. Importantly, for use in industrial processes, its autoignition temperature is 417 °C, higher than the other ether solvents and the two aliphatic hydrocarbons, hexane (225 °C) and cyclohexane (245 °C), which are commonly used in industrial applications. Although its lower explosion limit (LEL), expressed as a volume percent with the assumption of it being an ideal gas, is below that of toluene (TMTHF = 0.9%, toluene = 1.1%), its safety threshold in terms of mass is superior to toluene due to its higher molecular weight and lower density (see ESI† for example calculations).

Solubility properties of TMTHF

TMTHF also fulfilled the final criteria of this work: it has shown an ability to dissolve non-polar synthetic polyisoprene rubber, which only the most non-polar solvents are able to do. Although TMTHF is an ether by definition, its solvent and physical properties are more akin to those of toluene rather than other widely used ethers such as tetrahydrofuran (THF) and diethyl ether. A comparison of its Kamlet–Abboud–Taft (KAT) parameters[39] and Hansen Solubility Parameters (HSP)[40] with other solvents is shown in Table 1.

KAT parameters consist of three parameters which are determined by measuring the absorbance of dyes in the presence of the test solvent.[39,41] α is a measure of hydrogen-bond donating ability (acidity);[42] β is a measure of hydrogen-bond accepting ability (basicity);[43] and π^* is a combined measure of polarity and polarizability.[44] All the solvents shown in Table 1 are aprotic which is reflected in their α values of zero. Like the other ethers, TMTHF has high β (0.77) due to the lone pairs of electrons on the ethereal oxygen, while the hydrocarbons in contrast have low β values. TMTHF has a low π^* (0.35), similar to diethyl ether, while toluene's high polarizability due to its aromatic ring results in an elevated π^* compared to the aliphatic hydrocarbons. Overall, KAT parameters suggest that TMTHF should behave like a typical ether solvent but interestingly, its HSPs and its performance in some synthetic reactions, described later, indicate that this is not the case.

HSPs are determined by group contribution theory and describe the characteristic solubility of a molecule using three parameters in a similar way to KAT. Instead of one parameter to represent both polarity and polarizability as in KAT, the dispersion forces (from which polarizability can be calculated) and polarity are represented as two separate parameters, δ_D and δ_P. In addition, there is only one parameter to represent total hydrogen-bonding ability, δ_H. By plotting a molecule's HSPs on three axes, a three-dimensional map is generated from which solvation power can be easily visualized relative to other solvents. HSP theory follows the principle of "like dissolves like", where solvents tend to be able to dissolve nearby solutes on the HSP map and hence, two solvents with similar HSP's are more likely to have similar solvation power.[40] Combining the square of the three HSP's gives the square of the Hildebrand parameter, δ [eqn (4)]. The Hildebrand parameter is a more primitive measure of overall polarity and is equal to the square root of cohesive energy density (CED) [eqn (5)]. CED is a measure of a substances self-association. Increased molecular polarity and hydrogen-bonding results in increased CED and therefore, a larger Hildebrand parameter.

$$\delta^2 = \delta_D{}^2 + \delta_P{}^2 + \delta_H{}^2 \tag{4}$$

$$\delta = [(\Delta H - RT)/V]^{0.5} \tag{5}$$

It can be seen in Table 1 that HSP describes TMTHF's solvation power differently to KAT. While KAT describes TMTHF to be like other ethers, HSP suggests that the solvation power of TMTHF is more like toluene, an aromatic solvent free of heteroatoms (Fig. S4, ESI†). As expected, the hydrogen-bonding ability, δ_H, of the traditional ethers is high, due to their basic ethereal oxygens, which is consistent with KAT. However, TMTHF has been assigned a low δ_H, which is more characteristic of hydrocarbons.

TMTHF's molecular structure and electrostatic potential (ESP) map can help to explain this difference between HSP and KAT (Fig. 2).[45] The areas coloured red on the ESP map are areas of high negative charge density, the areas coloured off-white are positively charged while blue represents non-polar regions. Red areas can be seen on all the ethers shown. This is due to the lone-pairs of electrons on their ethereal oxygens, which are the source of their high β. While red areas on TMTHF indicate the presence of hydrogen-bond accepting lone pairs (in agreement with its high β in KAT), it can be seen that access to the lone pairs is sterically inhibited by the four adjacent methyl groups. This results in reduced hydrogen-bond accepting ability which is consistent with HSP.

The low Hildebrand parameter of TMTHF is as a result of both its low δ_H [from eqn (4)] and its low CED [from eqn (5)]. Although CED has not been measured, the lack of polarity and the steric hindrance to hydrogen bonding ability would be expected to be the main causes of its low value.

Overall, while high hydrogen-bond accepting ability is present in TMTHF, shown by its high β, steric hindrance caused by the four methyl groups inhibits this interaction. To confirm its suitability as a replacement for hydrocarbon as opposed to ether solvents, TMTHF has been tested as a solvent in several chemical reactions. Specific reactions were selected where the solvents basicity is known to contribute significantly, both positively and negatively. It has transpired that HSP's description of TMTHF's solvation power is more indicative of its performance than KAT's.

Fischer esterification and amidation reaction testing

It has previously been shown that the reaction rate of the catalyst-free Fischer esterification of butanoic anhydride with 1-butanol to produce butyl butanoate (Fig. 3) and the catalyst-free amidation of 4-phenylbutanoic acid with benzylamine to produce *N*-benzyl-4-phenylbutanamide (Fig. 4) are enhanced by solvents with a low basicity, β, by the use of linear solvation energy relationships (LSER).[11]

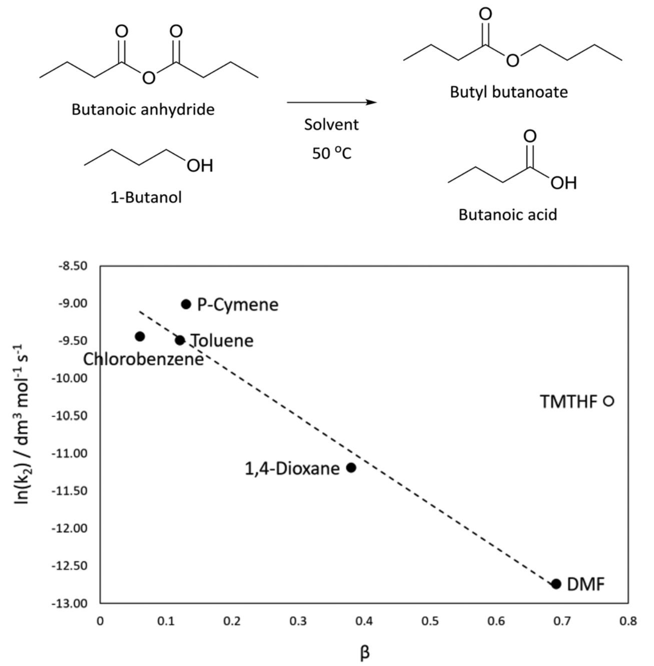


Fig. 3 Fischer esterification reaction scheme and LSER graph.

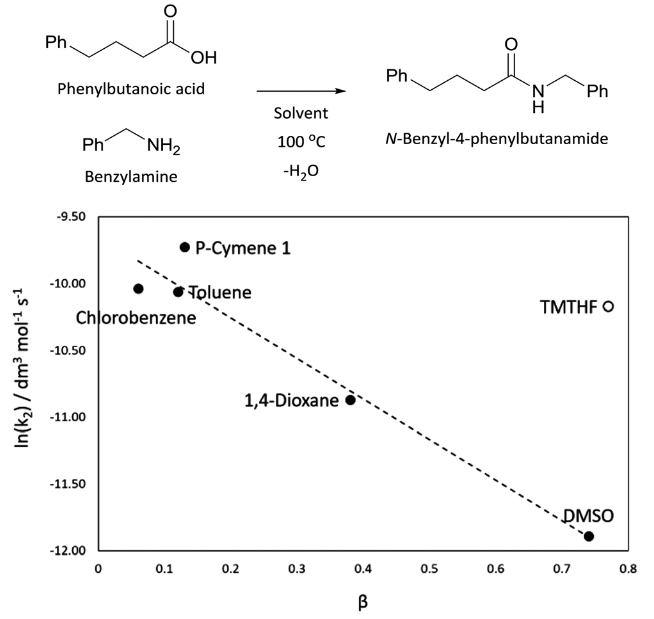


Fig. 4 Amidation reaction scheme and LSER graph.

The α and π^* parameters were found not to be statistically significant in these reactions. The use of TMTHF as the reaction solvent breaks from the trend observed by Sherwood *et al.* in both reactions.

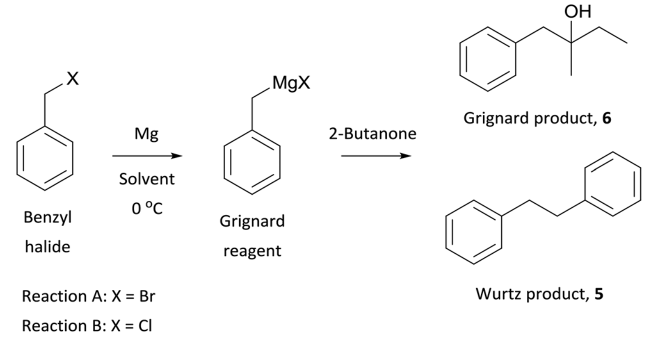
It can be seen in Fig. 3 and 4 that the rates of both reactions when using TMTHF as the solvent were more comparable to that of high-performing toluene and *para*-cymene, than those of either dimethylformamide (DMF), a solvent with a similarly high β, or 1,4-dioxane, a traditional ether. This supports the hypothesis that TMTHF's high β is, in practice, sterically impeded by the four methyl groups, resulting in a solvent which is more similar to the non-polar solvents toluene and *para*-cymene, both of which can promote Fischer esterification and amidation reactions better than normal ethers.

Grignard reaction testing

TMTHF's disparity from other ethers is further demonstrated by its inability to form some Grignard reagents. This is shown in the Grignard reaction between benzyl halides and 2-butanone (Table 2). These reaction were chosen as they are known to proceed to varying degrees using different ethers.[46] 2-MeTHF was more selective for the Grignard product, **6**, while THF was more selective for the Wurtz product, **5**, in reactions A and B.

TMTHF would be expected to perform as well as the traditional ethers based on its KAT parameters. However, like toluene, it was shown to be unable to promote the reaction. Despite the strong Lewis basicity of TMTHF, the steric hindrance of its four bulky methyl groups likely inhibit the lone pair on the ethereal oxygen from solubilizing the magnesium halide of the Grignard reagent, preventing its formation and the subsequent reaction from taking place. Although this is not a favourable result for a chemist who wishes to perform Grignard reactions in a new green solvent like TMTHF, it adds

Table 2 Results of the Grignard reactions in THF, 2-MeTHF, TMTHF and toluene



	Reaction A		Reaction B	
Solvent	Conv./%	6 : 5	Conv./%	6 : 5
THF	99	18 : 82	99	33 : 67
2-MeTHF	100	87 : 13	100	97 : 3
TMTHF	0	—	0	—
Toluene	0	—	0	—

weight to the claim that TMTHF behaves more like arene hydrocarbons than common ether solvents.

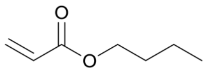
Radical-initiated vinyl polymerisation using TMTHF

It is not only in organic synthesis that TMTHF can be applied as a solvent; TMTHF has also been successfully used in radical-initiated polymerizations of vinyl monomers. A polymerization application which would particularly benefit from the use of a greener VNP such as TMTHF is the pressure-sensitive adhesive (PSA) industry where high molecular weight (M_w) polymers (>30 000 g mol^{-1}) are required.[47]

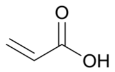
Currently, VNP solvents such as toluene and hexane are used in the production of PSAs. However as already mentioned, REACH restrictions are in place for the use of toluene in adhesives and spray paints (Annex XVII),[48] while hexane is a suspected CMR.[4] 2-MeTHF has previously been used as a greener alternative to THF in the production of anhydride-containing polymers for radiation sensitive compositions by radical polymerization.[49] However, the use of such solvents produced polymers with $M_w < 4000$ g mol^{-1}. Similarly low M_w's were obtained by the same authors when using THF. While low M_w's may be sufficient in photosensitive compositions, higher M_w's are required for PSA compositions.

The absence of alpha-protons on TMTHF means appropriately high M_w's can be achieved. This has been demonstrated in the polymerization of butyl acrylate and acrylic acid (Table 3). The monomers and dibenzoyl peroxide as the radical initiator were mixed in TMTHF at 70 °C under an inert atmosphere. The use of TMTHF yielded polymers with comparable M_w's to those obtained with toluene (501 000 and 509 000 g mol^{-1} respectively) as well as comparable solid content (27.25% and 31.00% respectively). Slight differences can be seen in the M_w distribution between TMTHF and toluene, with a narrower M_w distribution obtained in TMTHF (Fig. S14 and S15, ESI†). This demonstrates that TMTHF can influence the radical-initiated vinyl polymerization mechanism. Improved tack and adhesion compared to toluene was also observed in the final PSA. In contrast, low M_w's were observed when using 2-MeTHF as the solvent (9200 g mol^{-1}). This is assumed to be due to chain-transfer occurring between the polymer and solvent by the radical abstraction of the alpha-protons of the ether solvent. Hence, the desired high molecular weights could not be obtained. This is further evidence that TMTHFs unusual ether structure behaves significantly differently to traditional ethers.

Table 3 Results of radical polymerisation of butyl acrylate and acrylic acid using TMTHF, toluene and 2-MeTHF



Butyl acrylate
100 g



Acrylic acid
5 g

Polymer property	TMTHF	Toluene	2-MeTHF
M_w/g mol^{-1} [a]	501 000	509 000	9200
Solid content/%[b]	27.25	31.00	31.00
Adhesion/cN 20 mm^{-1} [c]	809	757	n/a[f]
Cohesion/days[d]	>10	>10	n/a[f]
Tack/g[e]	291	264	n/a[f]

[a] Measured by GPC at Nitto Europe. [b] Percent of solid polymer dissolved in solvent. [c] Measured by the breaking load test at Nitto Europe. [d] Measured by the shear adhesion test at Nitto Europe, values shown are the time of failure in days. [e] Measured by the rolling ball test at Nitto Europe. [f] Not measurable due to the low M_w obtained.

Ames mutagenicity testing and nearest neighbour toxicity prediction

The use of the Ames mutagenicity test to screen new molecules has recently been proposed as it is quick and cheap. Encouragingly, an Ames test of mutagenicity was carried out on TMTHF using two *Salmonella* bacterial strains, TA98 and TA100, where it was shown not to be mutagenic at concentrations up to 5 mg ml^{-1} (Fig. S5, ESI†).[12,50] Full toxicity testing will be required however before it can be authorized by REACH for production or use of more than 1 ton per year.[51] REACH encourages the use of predictive methods for initial toxicity screening of new molecules to avoid animal testing until it is necessary.[52] As such, a "nearest neighbour" prediction of toxicity is promising, as the nearest neighbour to TMTHF is 1,8-cineol. A nearest neighbour prediction makes estimations of molecular properties by using chemicals in a training set that are most structurally similar to the test chemical.[53] 1,8-Cineol is a terpene and is often used in fragrances and flavorings,[54] two applications where human exposure is high and where low toxicity is vital, making it an excellent comparison for a potential VNP solvent.[55] It has previously been suggested as a green solvent, but only due to its source from biomass and not in the context of its resistance to peroxide formation.[41] TMTHF and 1,8-cineol share several molecular properties: two quaternary alpha-carbons resulting in resistance to peroxidation; low octanol/water partition coefficients ($\log P_{(o/w)}$) of 1.92 and 2.28 respectively; similar KAT parameters; and similar molecular volumes of 151.1 cm^3 mol^{-1} and 167.5 cm^3 mol^{-1} respectively (predicted by HSPiP), all of which are shown in Table 1. The low $\log P_{(o/w)}$ of both 1,8-cineol and TMTHF compared to the alkanes and aromatics suggests a reduced likelihood of bioaccumulation in living organisms. In contrast, the significantly more chemically active alpha-protons in traditional ethers, demonstrated by their ability to form peroxides, means they will not give an accurate nearest neighbour toxicity prediction for TMTHF.

Acid stability

Acid stability tests were carried out on TMTHF using a range of acids with varying pK_a including glacial acetic acid, trifluoroacetic acid (TFA), *para*-toluenesulfonic acid monohydrate (PTSA), sulfuric acid (98%) and hydrochloric acid (37%). In these tests, TMTHF was stirred with a 1 mol% of the selected acid for 24 hours at room temperature or under reflux. The TMTHF used in the tests was >99% pure by ^1H NMR spectroscopy.

No noticeable colour change was observed after 24 hours at room temperature and no change could be detected by ^1H

NMR spectroscopy (Fig. S6, ESI†). When stirred under reflux, minor colour change from a clear colourless solution to a pale gold solution was observed in samples mixed with PTSA, sulfuric acid and hydrochloric acid. However, it is not certain that the colour change was a result of degradation of TMTHF or of some of the impurities which were initially present in the test solvent. ^{1}H NMR spectroscopy suggests the presence of some alkene impurities (~0.5%) in the test solvent prior to addition of acid, which would also be susceptible acid catalysed polymerisation *via* a carbocation intermediate and could result in colour change (Fig. S7, ESI†). Work is underway to further test ultrapure TMTHF to give a better understanding of its stability in acidic conditions, but early results are nevertheless promising.

These encouraging results suggest that TMTHF is suitable for reactions in acidic conditions at room temperature and that no significant degradation occurred when mixed with acid under reflux for 24 hours, which opens up potential applications as a medium in acid catalysis. In addition, the dangers associated with mixing acids with peroxides which form in traditional ethers are not present in TMTHF due to its inability to form peroxides. However, precautions must always be taken and so a peroxide test prior to the addition of any acid would always be advisable.

Green credentials

To date a solvent that is collectively green, volatile, non-polar and safe has eluded the chemical industry. Our initial study shows that TMTHF adheres to these criteria and is an ideal candidate to fill this important gap in the solvent space. TMTHF has a boiling point of 112 °C, a melting point below −90 °C, a very useful low polarity and is resistant to peroxide formation. The potentially renewable route to this molecule that utilizes clean synthetic methodologies (including catalysis and flow chemistry) make this a solvent with strong green credentials. This is further strengthened by the high AE of 96% and RME of 93% for its synthesis. TMTHF has passed an initial Ames test for mutagenicity, and nearest neighbour predictions of toxicity are promising due its structural similarity to 1,8-cineol, a component of many fragrances and flavorings.[54] However, full toxicity testing would need to be conducted before this solvent could be produced or used on a commercial scale. TMTHF's boiling point of 112 °C means it can be removed by evaporation with relative ease, a property which scores well in the recyclability segment of the GSK solvent guide.[7] It is immiscible with water, glycerol, dimethyl sulfoxide (DMSO), ethylene carbonate and propylene carbonate, thus opening up applications in liquid–liquid extraction. TMTHF therefore has the potential to further improve some processes in which a greener workup solvent is required.

Conclusions

TMTHF can be produced catalytically in a highly atom economical process by the ring closure of DMHDL, a diol which is currently produced industrially from acetylene and acetone. The process can be made sustainable with the use of renewable acetylene and acetone as drop-in replacements. Based on its structure, TMTHF is classed as an ether and its Kamlet–Abboud–Taft parameters demonstrate high hydrogen-bond accepting ability like traditional ethers. However, its Hansen solubility parameters are more like those of toluene. These similarities to toluene and disparities to traditional ethers have been confirmed by its performance in model Fischer esterification, amidation and Grignard reactions. Furthermore, TMTHF was shown to be a suitable solvent for radical-initiated polymerizations. It is inherently resistant to peroxide formation without the assistance of antioxidants, unlike other ethers such as THF, 2-MeTHF and CPME, allowing it to be used safely in the chemical industry. Finally, an Ames test using TA98 and TA100 *Salmonella* bacterial strains found TMTHF not to be mutagenic, further evidence of it being a safer solvent compared those it would replace. Preliminary acid stability tests suggest TMTHF can resist acid attack at room temperature and results are promising even under reflux. Such a solvent will create new opportunities for industry to improve the green credentials of a process with a safer renewable replacement for toluene and other widely used VNP solvents.

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