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FULL PAPER

A Family of Water Immiscible, Dipolar Aprotic, Diamide Solvents from Succinic Acid

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Abstract: Three dipolar aprotic solvents were designed to possess high dipolarity and low toxicity: *N*,*N*,*N*',*N*'-tetrabutylsuccindiamide (TBSA), *N*,*N*'-diethyl-*N*,*N*'-dibutylsuccindiamide (EBSA), *N*,*N*'-dimethyl-*N*,*N*'-dibutylsuccindiamide (MBSA). They were synthesized catalytically using a K60 silica catalyst in a solventless system. Their water-immiscibility stands out as an unusual and useful property for dipolar aprotic solvents. They were tested in a model Heck reaction, metal-organic framework syntheses, and a selection of polymer solubility experiments where their performances were found to be comparable to traditional solvents. Furthermore, MBSA was found to be suitable for the production of an industrially relevant membrane from polyethersulphone. An integrated approach involving in silico analysis based on available experimental information, prediction model outcomes and read across data, as well as a panel of in vitro reporter gene assays covering a broad range of toxicological endpoints was used to assess toxicity. These in silico and in vitro tests suggested no alarming indications of toxicity in the new solvents.

Introduction

Dipolar aprotic solvents such as *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylacetamide (DMAc) and *N*,*N*-dimethylformamide (DMF) have many important functions throughout the chemical industry, such as in polymer production,[1–3] organic synthesis,[4–7] graphene dispersion/exfoliation[8,9] and metal-organic framework (MOF) synthesis.[10] However, all are petroleum-derived and suffer from high reprotoxicity.[11–14] As such, all are listed as substances of very high concern (SVHC) by the European Union's regulation REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals),[15] meaning alternatives are urgently needed.[16]

Progress has been made in this regard in recent years; new methods of solvent design have been developed,[17–19] and new molecules and solvent systems have been discovered. For example, ionic liquids can act both as solvents and catalyst for some biphasic synthetic applications, potentially eliminating the need for dipolar aprotic solvents in some reactions.[20,21] Where a solvent is required, Cyrene (levoglucosenone-derived),[22] propylene carbonate (carbon dioxide-derived)[23–25] and gamma-valerolactone (5-(hydroxymethyl)furfural (HMF)-derived)[26,27] have demonstrated dipolarity in a variety of applications. *N*-Butylpyrrolidinone (NBP) is an amide solvent which has recently been developed by Eastman Chemical Company.[28] It is structurally similar to NMP, but contains an *n*-butyl group instead of a methyl group, which results in non-reprotoxicity.[29] However, while the *n*-butyl group eliminated reprotoxicity, it also reduced dipolarity compared to the traditional dipolar aprotic solvents.

The target of this work was to design a robust, bio-based or bio-derivable dipolar aprotic solvent that possesses high dipolarity and is non-reprotoxic. As such, three new solvents have been proposed - *N*,*N*,*N*',*N*'-tetrabutylsuccindiamide (TBSA), *N*,*N*'-diethyl-*N*,*N*'-dibutylsuccindiamide (EBSA), *N*,*N*'-dimethyl-*N*,*N*'-dibutylsuccindiamide (MBSA). They have been synthesized using clean synthetic methodologies, including a reusable heterogeneous catalyst, and have been characterized for their physical and solubility properties. In addition, they have been application tested in a model Heck reaction, metal-organic framework (MOF) synthesis and solubility testing of industrially relevant polymers (Polyvinylidene fluoride (PVDF), polyethersulphone (PES) and polyamide imides (PAIs)) where they were shown to perform comparably and, in some cases, better than traditional dipolar aprotic solvents. In other cases, interesting results were obtained due to the water immiscibility of the succindiamides.

Finally, the effect of *n*-butyl groups on diamides in terms of toxicity was examined. For this purpose, the compounds were analyzed using an integrated testing strategy combining in silico predictions with in vitro reporter gene assays. The in silico

prediction of toxicity of the compounds is a useful first step of toxicity analysis and focused on the human health endpoints decisive to authorization and restriction under REACH. This includes carcinogenicity (C), mutagenicity (M), and reproduction toxicity (R), and on another health endpoint considered critical in this respect, skin sensitization (S). The CALUX® battery of in vitro reporter gene assays contains a range of specific tests that can be used for assessing chemical safety. It consists of 18 human cell-based assays, each able to measure chemical interactions between a test compound and a specific nuclear receptor or cell signaling pathway.[30] The use of these contrasting but complementary screening approaches aims to generate a more robust assessment of potential safety issues.

Results and Discussion

Solvent design

Inspired by NBP's lower reprotoxicity compared to NMP,[28] a range of similarly non-reprotoxic, but more polar, molecules were sought. Three molecules were designed which targeted these solvent properties.

It is not clear why, but as the *n*-butylamide group on NBP is the only structural difference between NBP and NMP, it is this functionality that reduces reprotoxicity compared to the methylamide group of NMP. However, the consequence of the *n*-butylamide group is an undesired lower dipolarity compared to traditional dipolar aprotic solvents. Therefore, it was hypothesized that by generating molecules that contain two *n*-butylamide groups (*N*,*N*'-dibutyldiamide), a combination of low reprotoxicity and high polarity could be achieved (Figure 1).

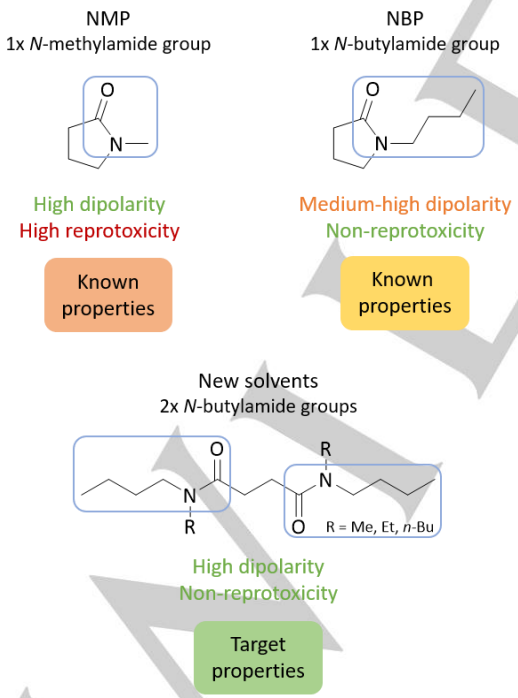
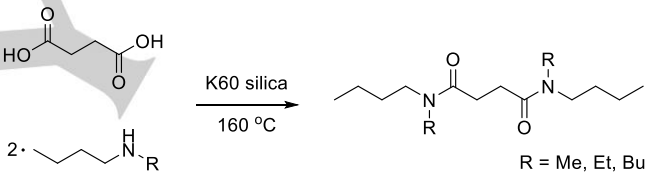


Figure 1. The hypothesised effect on polarity and toxicity of having two *n*-butylamide groups on one molecule.

Succinic acid is one of the top value-added chemicals from biomass proposed by the US DOE in 2004.[31] Since then it has been established as one of the most promising bio-based platform chemicals[32] with several companies targeting its commercialization.[33–36] Succinic acid can be produced either by the fermentation of sugars or by the oxidation of levulinic acid.[37] Being a 1,4-diacid, it was identified as an ideal chassis onto which *N*,*N*'-dibutyldiamides can be built by reacting with alkylbutylamines (Figure 1). In addition, alkylbutylamines can be easily produced from biomass by the amination of bio-butanol, bio-ethanol and bio-methanol.

Synthesis of *N*,*N*'-dialkyldibutylsuccindiamides

The three new *N*,*N*'-dialkyldibutylsuccindiamides were first synthesized using succinyl chloride and the corresponding secondary amine as a proof of concept and to measure solvent properties (Table 1, Entries 5-7). Upon confirmation that the solvents were indeed dipolar, the synthesis was attempted by the amidation of succinic acid with the corresponding secondary amines (Scheme 1). K60 silica calcined at 700 °C (K60-700) has previously been demonstrated to catalyze the amidation of carboxylic acids with amines.[38] K60-700 is a robust solid catalyst which is easy to produce, is non-corrosive, and can be recovered from the reaction mixture and reused after calcination again at 700 °C.[38] As such, it was employed in the production of the new amides.



Scheme 1. The syntheses of *N*,*N*'-dialkyldibutylsuccindiamides from succinic acid.

Table 1. Reaction yields for the synthesis of *N*,*N*'-dialkyldibutylsuccindiamides.

Entry	Starting material	Product	Yield [%]
1	Succinic acid	TBSA	45[a]
2	Succinic acid	EBSA	31[b]
3	Succinic acid	MBSA	<10[c]
4	Succinic acid	MBSA	53[d]
5	Succinyl chloride	TBSA	63[e]
6	Succinyl chloride	EBSA	82[e]
7	Succinyl chloride	MBSA	70[e]

[a] Open system, reflux conditions (~160 °C), 18 hours. [b] Open system, reflux conditions (~110 °C), 18 hours. [c] Open system, reflux conditions (~90 °C), 18 hours. [d] Closed system, increased pressure (180 °C), 18 hours. [e] N_2 flow, no temperature control (<35 °C), 18 hours, DCM solvent. See ESI for detailed experimental procedures.

The reactions were carried out in a solventless system, with the amines being used in a large excess (15:1 mol ratio, amine/succinic acid). Due to the higher boiling points of dibutylamine (160 °C) and ethylbutylamine (109 °C) compared to methylbutylamine, higher reflux temperatures could be obtained.As such, the synthesis of the corresponding amides, *N*,*N*,*N*',*N*'-tetrabutylsuccindiamide (TBSA) and *N*,*N*'-diethyl-*N*,*N*'-dibutylsuccindiamide (EBSA), could be carried out under reflux and atmospheric pressure, with yields of 31% and 45%respectively (Table 1, Entries 1 and 2). The lower boiling point of methylbutylamine (90 °C) meant that the synthesis of *N*,*N*'- dimethyl-*N*,*N*'-dibutylsuccindiamide (MBSA) only achieved a very low yield after 18 hours (<10%) (Table 1, Entry 3). As such, the reaction was instead carried out in a closed system under elevated pressure to allow higher temperatures to be reached. This was achieved when the reaction was carried out 180 °C, with a yield of 53% being obtained (Table 1, Entry 4). Although the yields are moderate, unreacted starting material can be easily separated using Kugelrohr short-path distillation at 160 °C and 1 mbar and recycled back into the system for reuse. A small amount of the cyclic imide was produced as a side product in all cases, but this was also easily removed by distillation and can be recycled back into the system to undergo secondary amidation.

This process has the potential to be carried out in continuous flow. For a flow process to be possible, both reactants (acid and amine) must be in a liquid phase, as the K60 silica catalyst is a solid. However, succinic acid is a solid and is not soluble in the amines. As such, potential for the succindiamide solvents to be used as the solvent in their own synthesis was examined. First, the solubility of succinic acid in the corresponding succindiamide was examined. It was found that 10 wt% succinic acid was soluble in MBSA at room temperature, allowing such a flow process to be investigated. However, succinic acid was largely insoluble in EBSA and TBSA. Succinic anhydride was then examined as an alternative to succinic acid and was found to be soluble in each of the succindiamides at 10 wt%. Succinic anhydride provides the added benefit of being reactive with the amines, forming the succinamic acid (acid-amide), at room temperature without the need for a catalyst. Succinamic acid can potentially react with another equivalent of amine in the same conditions to produce the succindiamides. A full investigation into the flow synthesis of the new solvents is ongoing.

Characterization of new solvents

Solvents properties are shown in Table 2. The boiling points of the succindiamides are higher than the traditional dipolar aprotics, being distilled in vacuo at 160 °C, while their melting points are significantly lower (-76 to -79 °C). Their densities are similar both to water and the traditional dipolar aprotics solvents.

NBP was found to be miscible with both water and hexane. This is demonstrated by their octanol/water partition coefficients. The succindiamides have large, positive Log $P_{(o/w)}$ values, meaning they favor the organic layer in an octanol/water biphasic system and are therefore more lipophilic.[39] In contrast, the traditional dipolar aprotics have large, negative Log $P_{(o/w)}$ values so are more hydrophilic. NBP displays intermediate properties, with a Log $P_{(o/w)}$ of 0.99, meaning it prefers the organic phase but not enough to make it immiscible with water. Importantly, none of the succindiamide solvents have a Log $P_{(o/w)}$ above 4, the value

Table 2. Properties of the new solvents in comparison with traditional solvents.

Solvent property	TBSA	EBSA	MBSA	NBP	NMP	DMF	DMAc
M_w [g mol^{-1}]	340.55	284.44	252.36	141.21	99.13	73.09	87.12
b.p. [°C]	>250[a,b]	>250[a,b]	>250[a,b]	241[c]	202[d]	153[d]	166[d]
m.p. [°C]	-76[e]	-76[e]	-79[e]	<-75[c]	-24[d]	-60[d]	-20[d]
Density [g mL^{-1}]	0.96[a]	0.97[a]	0.99[a]	0.96[c]	1.03[d]	0.94[d]	0.94[d]
Mol. Vol. [cm^{-3} mol^{-1}]	368.3[f]	299.6[f]	266.3[f]	149.1[f]	96.6[f]	77.4[f]	93.0[f]
Log $P_{(o/w)}$	3.77[a]	2.72[a]	1.65[a]	0.99[a]	-0.38[d]	-1.01[d]	-0.77[d]
δ_D [MPa$^{-0.5}$]	17.2[f]	17.2[f]	17.5[f]	17.4[f]	18.0[f]	17.4[f]	16.8[f]
δ_P [MPa$^{-0.5}$]	9.0[f]	10.4[f]	11.0[f]	6.7[f]	12.3[f]	13.7[f]	11.5[f]
δ_H [MPa$^{-0.5}$]	2.9[f]	3.3[f]	7.5[f]	5.2[f]	7.2[f]	11.3[f]	9.4[f]
α	0.00[g]	0.00[g]	0.00[g]	0.00[g]	0.00[g]	0.00[c]	0.00[c]
β	0.91[h]	0.91[h]	0.82[h]	0.92[h]	0.75[c]	0.71[c]	0.73[c]
π^*	0.63[e]	0.67[e]	0.78[e]	0.77[e]	0.90[c]	0.88[c]	0.85[c]
Water miscibility	No[a]	No[a]	No[a]	Yes[a]	Yes[a]	Yes[a]	Yes[a]
Hexane miscibility	Yes[a]	Yes[a]	Yes[a]	Yes[a]	No[a]	No[a]	No[a]

[a] This work. [b] Distilled by Kugelrohr short-path distillation at 160 °C and 1 mbar. [c] Sherwood *et al.*[25]. [d] Data obtained from PubChem. [e] Measured by differential scanning calorimetry. [f] Calculated using HSPiP (version 5.1.08). [g] Assumed value. [h] This work, using *N*,*N*-diethyl-4-nitroaniline and 4-nitroaniline dyes. [i] This work, using *N*,*N*-diethyl-4-nitroaniline dye.

which has been set as a threshold for bioaccumulation in the environment. The Hansen Solubility Parameters (HSP)[40] and the Kamlet-Abboud-Taft (KAT) parameters of the new solvents wereobtained.[41–43] HSP characterizes solvents in terms of their dispersion forces (δ_D), dipolarity (δ_P) and hydrogen-bonding ability (δ_H). Higher values indicate stronger intermolecular interactions. KAT parameters provide similar information but thedipolarity and polarizability (dispersion forces) are combined in one parameter (π^*) while hydrogen-bond donating ability (α) andaccepting ability (β) are separated. HSP values are predicted using HSPiP software while KAT parameters are calculated by measuring the absorbance of dyes which are dissolved in the solvent.

Table 2 shows that the δ_D of each succindiamide is comparable to the traditional dipolar aprotics (17.2-17.5 $MPa^{-0.5}$), likely due to the common dominant amide functionality across all molecules. The δ_P of each candidate is in the range of 9.0-11.0 $MPa^{-0.5}$, which is slightly lower than the traditional dipolar aprotics whose polarity ranges from 11.5-17.4 $MPa^{-0.5}$, but higher than the other butylamide, NBP (6.7 $MPa^{-0.5}$). MBSA provides the highest dipolarity of the succindiamides due to its shorter alkyl chains, followed by EBSA and MBSA. Interestingly, each of the succindiamides, particularly TBSA and EBSA, possess far lower δ_H than traditional dipolar aprotics. This is consistent with the Log $P_{(o/w)}$ values and their immiscibility with water but miscibility with hexane, a very unusual property for polar solvents (Table 2).
As none of the succindiamides are protic, α is 0.00 in all cases. The succindiamides, along with NBP, have higher β values than the methylamides NMP, DMF and DMAc. MBSA, which is the least lipophilic of the succindiamides, falls in between the traditional butyl and methylamides in terms of β. Higher β values are due to the greater electron-donation of the butyl chains compared to the methyl chain. This conflicts with the HSP and Log $P_{(o/w)}$ assessment of the succindiamides, as a higher β would suggest an increased water miscibility. This suggests that either steric effects due to the long butyl chains block access to the amide functional groups, or that the average β across the larger succindiamide molecule is reduced compared to the traditional solvents.

The dipolarity/polarizability, π^*, of each of the succindiamides is lower than traditional dipolar aprotics and closer to the butylamide, NBP. As the KAT description of polarity is in contrast with the HSP description, several application tests were carried out to assess the performance of the succindiamides in comparison to the traditional solvents.

Application testing

To demonstrate the applicability of the new succindiamide solvents, they underwent a selection of solubility tests on industrially relevant polymers, PES membrane fabrication, a model Heck reaction[24] and as a solvent for metal-organic framework (MOF) synthesis which are described in the following sections.[44].

Industrially relevant polymer dissolution study

Polar aprotic solvents play a significant role in the production of a number of articles where dissolution of specific polymers is required. Currently these processes predominantly use the solvents NMP, DMAc and DMF, and as such, alternatives are required. Three polymers are closer evaluated in this work: polyamide imides (PAIs), polyethersulfones (PES) and polyvinyl difluoride (PVDF). Polyamide imides (PAIs) were first developed in the 1950s and became commercially available in the 1960s for use in injection molding.[45] When requiring solvent application, they have been applied as a hard coating for kitchen appliances, a laminating resin and most profusely as a wireenamel.[46] The PAI utilized in this work is Torlon AI-10, developed specifically for film forming applications.[47]

Table 3. Results of polymer dissolution at 10 wt% PVDF, PES and PAI in MBSA, EBSA, TBSA and NBP.

Solvent	PVDF[a]	PES[a]	PAI[a]
MBSA	Soluble[b]	Soluble	Soluble
EBSA	Soluble[b]	Partially soluble	Soluble[c]
TBSA	Soluble[b]	Insoluble	Soluble[c]
NBP	Soluble[b]	Soluble	Soluble

[a] Dissolution carried out at 80 °C with agitation for 1 hour. [b] Formed gel upon cooling. [c] Precipitation upon cooling.

Polyethersulfone (PES) is a high-temperature engineering thermoplastic principally used in formation of membranes due to its excellent physical characteristics and the degree of control that can be achieved through modification of the casting system.[48] The PES investigated in this work is Ultrason E3020.[49] Finally, polyvinyl difluoride (PVDF) is a chemically and thermally stable but electronically active polymer.[50] PVDF has many applications, including in membrane formation,[51] medical sensors[52,53] and as a binder in lithium-ion batteries.[54,55] The grade of PVDF applied here is Solef 5130 widely utilized in battery production.[56] All polymer dissolution studies were carried out at 10 wt% loading (200 mg in 2 g of solvent) and heated to 80 °C with agitation by a magnetic stirrer bar, before being left to cool. MBSA, EBSA, TBSA and NBP (Table 3) were used as the test solvents.

All four solvents were able to dissolve PVDF at dissolution temperature but produced a gel upon cooling. Hence, the stirrer bars could not be removed (Figure S1, ESI). Only MBSA and NBP fully dissolved PES, partial dissolution was observed with EBSA and no interaction was observed with TBSA. Finally, full dissolution of PAI was observed with MBSA and NBP, while TBSA and EBSA saw some polymer precipitate out of solution upon cooling. The results suggest these novel polar aprotics would all be suitable for use with PVDF and PAI, while MBSA could also be used in applications of PES. As such, membrane formation in a non-solvent induced phase separation (NIPS) process was chosen as an application to test the performance of MBSA with PES.

PES membrane fabrication

The demand for clean water or controlled aqueous systems requires efficient treatment methods. Membrane filtration offers such a solution. Many polymers have been reported for membrane fabrication, such as cellulose acetate, polyvinyl difluoride (PVDF), polyvinyl alcohol (PVA) and polyethersulfone (PES). PES has emerged as particularly effective polymer for membrane fabrication as it offers high thermal, hydrolytic and chemical stability.

Fabrication of PES membranes are traditionally done using dipolar aprotic solvents such as NMP and DMSO. As the solvent represents the largest contributor of waste in the production process, greener alternatives are required.[57] Recently, the new green solvent, Cyrene, has been demonstrated to produce high

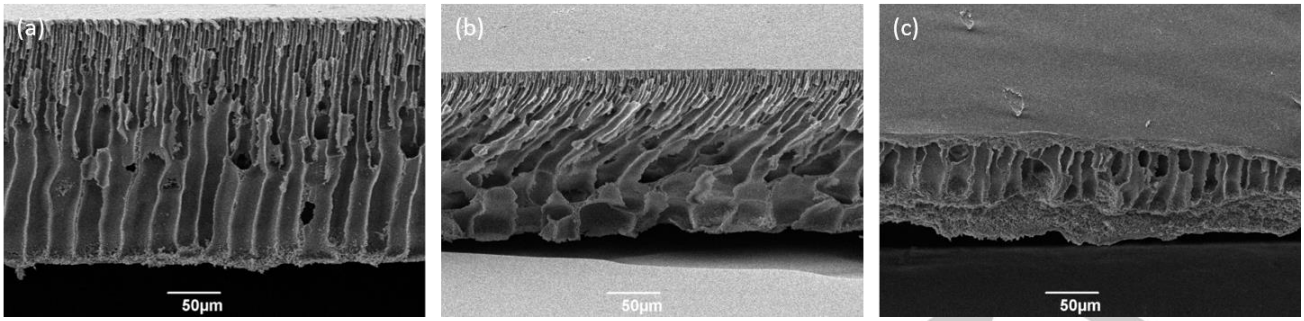


Figure 2. Scanning Electron Microscopy images of cross-section of the membranes casted using (a) water, (b) TMO and (c) hexane as non-solvent.

quality PES membranes.[58,59] As MBSA was found to be able to dissolve PES, it was tested for its ability to fabricate a PES membrane. The varying affinities of MBSA/PES casting solutions for solvents causes changes in morphology, leading to different performances of the produced membranes.

The membrane production process involves applying a degassed 10 wt% PES casting solution onto a glass plate. The glass plate is then submerged in a miscible non-solvent to quickly remove the solvent, leaving a porous membrane. Traditionally, a dipolar aprotic solvent such as NMP is used as the solvent, which is removed by water as the non-solvent. As MBSA is immiscible with water and miscible with non-polar solvents, a reversed approach was adapted for this work. Two non-polar non-solvents were chosen for this study, hexane and 2,2,5,5-tetramethyloxolane (TMO),[60] as both are miscible with MBSA. Water was also included in the study for comparison.

Demixing the PES/MBSA cast in hexane as the non-solvent resulted in partial dissolution of the polymer (Figure 2, c). As a result, the morphology of the membrane was negatively affected, with dense regions at the surfaces. In addition, significant losses to the bulk solution of non-solvent were also observed. Interestingly, a greener alternative to hexane, TMO, performed far better (Figure 2, b). It did not dissolve the polymer and allowed demixing of the mutually soluble MBSA, generating a finger-like porous structure with large macro-voids at the bottom. Using water as the non-solvent generated a similar morphology to when TMO was used, but with slightly smaller macro- voids at the bottom surface (Figure 2, a). Both morphologies are consistent with those previously reported in the literature.[48,58,59] The performance of water as the non-solvent was surprising as MBSA and water are immiscible. However, upon closer inspection, it was observed that water is partially soluble in MBSA (Figure S2, ESI). As the non-solvent is in a large excess, effective demixing of the MBSA by water was achieved in this system.

The porosity of the PES/MBSA membranes produced using TMO and water as non-solvents were comparable to those previous reported in the literature and provide a fully green solvent system for their production.

Metal-organic framework (MOF) synthesis

Metal-organic frameworks (MOF) are porous materials which have been demonstrated to be useful for many applications, from catalysis[61] and gas absorption[62] to electronics[63] and sensors.[10] As such, they can potentially be a vital cog in the green chemistry wheel. To be considered fully "green", they must first be synthesized in a green way. Many MOFs are simply made by mixing the components together in a suitable solvent, so the solvent properties are the predominant factor in the greenness of the synthesis.[44]

Recently, the green dipolar aprotic solvent Cyrene has been demonstrated to be a suitable solvent to replace *N*,*N*-dimethylformamide (DMF) for the synthesis of a selection of MOFs.[44] Therefore, MOF synthesis could be an example of a promising application for the new succindiamide solvents. Two MOFs were chosen as probes, HKUST-1 and ZIF-8, as comparable data was already available for them.[44] Their synthesis, using the succindiamides as the solvent in comparison to DMF was investigated.

Microwave heating was used in the preparation of the MOFs as an alternative to conventional heating. This shortened the MOF preparation time from 18 hours and 10 hours for HKUST-1 and ZIF-8 respectively to 20 minutes in the microwave.[44] While this already improved the greenness of the synthesis of the MOFs, more importantly, it demonstrated that the three new succindiamide solvents can absorb microwave energy, opening opportunities in other applications.

Figure 3 shows the powder XRD patterns for HKUST-1 (A) and ZIF-8 (B) MOFs produced in DMF, MBSA, EBSA and TBSA. For HKUST-1, it can be seen that the powder XRD pattern is almost identical in each solvent, indicating that the HKUST-1 crystal structure is successfully synthesized in all new solvents. The peak width in the crystals synthesized in EBSA were slightly broader, indicating a marginally smaller particle size. The intensity of the {222} reflection in MBSA (11.4° 2θ) was similar to DMF, but lower in EBSA and TBSA. A lower intensity in {220} (9.4° 2θ) but a greater intensity in {200} (6.5° 2θ) was observed in all of the succindiamides compared to DMF, indicating a common preferential growth in the succindiamides that differed with DMF. The BET surface areas of HKUST-1 produced in the different solvents is shown in Table 4 (isotherms can be seen in Figure S20, ESI). EBSA generated the highest BET surface area (1,116 m2 g-1) and was almost identical to that of DMF (1,111 m2 g-1), while results for MBSA (981 m2 g-1) and TBSA (914 m2 g-1) were slightly lower.

For ZIF-8, only TBSA was successful in synthesizing the MOF with the same XRD pattern as in DMF (Figure 3, B). The {110} (7.3° 2θ) peak is weak in EBSA and absent in MBSA, while the {200} (10.3° 2θ) reflection is also weak in MBSA. The remaining pattern at higher 2θ values closely resembled those in DMF. The porosity of the MOFs followed an opposite trend with MBSA (1,137 m2 g-1) producing a comparable BET surface area to DMF (1,182 m2 g-1), while EBSA (667 m2 g-1) and TBSA (314 m2 g-1) produced lower BET surface areas.

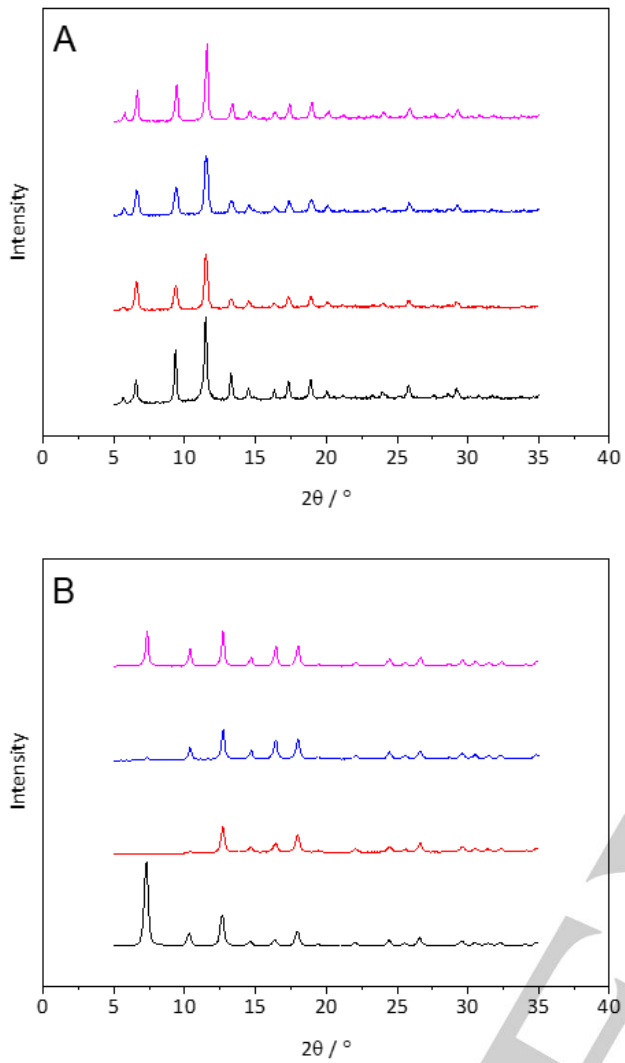


Figure 3. XRD spectra of HKUST-1 (A) and ZIF-8 (B) synthesised in DMF (black), MBSA (red), EBSA (blue) and TBSA (pink).

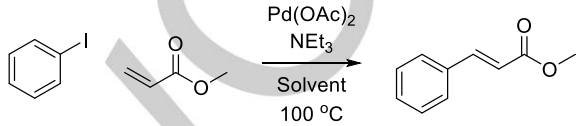
Table 4. BET surface area and yields of the two MOFs synthesised in four solvents.

Solvent	HKUST-1 [m^2 g^{-1}]	ZIF-8 [m^2 g^{-1}]
MBSA	981	1,137
EBSA	1,116	667
TBSA	914	314
DMF	1,111	1,182

Thermogravimetric analysis (TGA) traces of the four ZIF-8 samples suggests that the reason for the lower BET surface areas of ZIF-8 synthesized in TBSA and EBSA is that residual solvent may have been trapped in the pores (Figure S21, ESI). Mass losses at ~400 °C in the EBSA sample and ~500 °C for the TBSA sample suggests the evaporation of trapped solvent. These mass losses were not observed in the DMF or MBSA samples.

Heck reaction

The Heck reaction is a pharmaceutically relevant reaction that is also dependent on solvent polarity, being promoted in polar solvents.[4,24] As such, succindiamides are applied as solvents for this reaction in order to evaluate their suitability for Heck, or indeed C-C-coupling reactions in general. A model Heck reaction between methyl acrylate and iodobenzene was carried out in different solvents (Scheme 2). Using DMSO as a solvent, the reaction order was confirmed to be first-order with respect to methyl acrylate.[64] A linear solvation-energy relationship (LSER) of the natural log of the first-order rate constant (ln(k_1)) versus π^* of a range of solvents can be seen in Figure 4, and illustrates the rate dependence on solvent polarity of the model Heck reaction.



Scheme 2. The Heck reaction between iodobenzene and methyl acrylate.

MBSA was particularly effective for this reaction, performing comparably to DMSO and better than NBP. TBSA and EBSA fitted the trend and performed according to their polarity. Interestingly, during the reaction it was observed that the triethylammonium iodide salt formed during the coupling precipitated out of solution in the three succindiamides in the course of the reaction. In contrast, the traditional dipolar aprotic solvents kept the ammonium salt in solution throughout the reaction. This is potentially very useful as it makes product isolation easier compared to traditional dipolar aprotic solvents. Again, this highlights the lack of ionic character and hydrogen bonding ability in the succindiamides, an unusual property which may be beneficial in many future chemical processes.

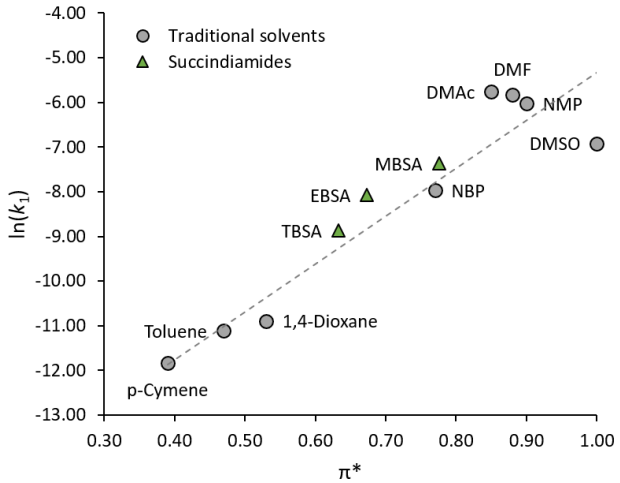


Figure 4. LSER showing the reaction rates of the Heck reaction in a range of solvents.

Toxicity testing

To examine the effect of the *N*-butylamide group in comparison to the *N*-methylamide group in terms of their toxicities, an integrated

approach using both in silico and in vitro assessments was carried out. Detailed materials & methods can be found in the ESI.

The in silico approach consisted of gathering any available adequate experimental toxicity data for C (carcinogenicity), M (mutagenicity), R (reprotoxicity) and S (skin sensitization) endpoints, performing QSAR model-based predictions using VEGA, DTU, and Toxtree tools, and exploring read-across from structural similar with adequate experimental toxicity data or available QSAR predictions (in DTU).

The in vitro approach utilised the CALUX® battery of 18 in vitro reporter gene assays, covering a broad range of toxicological endpoints, providing information on the propensity of a test compound to trigger certain molecular events which could result in adverse health effects. This panel has been used successfully in several large screening programs, such as the EU Framework program (FP) ReProTect and ChemScreen projects, which were both specifically directed at the detection of reproductive toxicity.[65–69]

Complementarity was based on the notion that the in silico models are using structural alerts of chemicals to predict biological behavior, while the in vitro methods use biological pathways to assess chemical behavior in a more unbiased manner.

In silico toxicity analysis

If experimental data of sufficient quality was available for the candidate compound, these were taken as decisive for the health endpoint of that compound, i.e. indicating the presence or absence of specific hazardous properties. These data therefore overruled the in silico model predictions and prevented any further read-across explorations. Such was the case for NBP: experimental data for M, R, and S were available, and adequate, and all indicated that NBP was negative for these endpoints. For NBP, therefore, in silico predictions were only performed for C, which was also found to be negative. This is illustrated in Table 5 by green colored cells for C, M R, and S for NBP. Table 5 also shows NMP as positive for R, and negative for C, M, and S.

No experimental data were available for any of the butylsuccindiamides in this work and thus, QSAR model predictions were generated for all four toxicological endpoints. As DTU predictions for these specific butylsuccindiamides were not available, predictions that were available for the structural analogues tetramethyl-, and tetraethylsuccindiamides (with CAS 7334-51-2, and 22692-57-5, respectively) were used instead: both were predicted to be negative for C and R, while predictions for M (chromosomal aberrations) and S where out of domain.

VEGA predictions for the butylsuccindiamides were out of domain for C, negative for M (i.e. for bacterial mutagenesis), negative for R, and not trustworthy for S. The overall conclusion for M, combining predictions from DTU and VEGA, was inconclusive, reflected by the grey color in Table 5. As the succindiamide structure is not an alert for S[70], this endpoint is predicted negative as well; indicated by the green color. Thus, Table 5 shows that NBP, the candidate that is structurally closest to NMP, received a negative (green) score for all CMR and S endpoints, based on reliable experimental data ("exp") for M, R and S, and on an in silico prediction for C. The CMRS assessment for the other three candidate compounds MBSA, EBSA, and TBSA, structurally less close to NMP, but structurally closely related among themselves, also showed negative predictions for all four endpoints

Table 5. CMR and S assessments for NMP and its candidate substitute compounds.

Compound	C	M	R	S
NMP	exp	exp	exp	exp
NBP		exp	exp	exp
MBSA				
EBSA				
TBSA				

Green: absence of property; Red: presence of property; Grey: no prediction possible. "exp": conclusion based on reliable experimental data.

In vitro reporter gene assay analysis

NMP, NBP, MBSA, EBSA and TBSA were analyzed on a panel of 18 reporter gene assays, covering different toxicological endpoints (Table 6). All compounds showed cytotoxicity in the millimolar range; for the succindiamides the lowest effect concentration (LEC), which reflects the compound's potency, increased with increasing chain length from 5.0 mM to 0.4 mM. The lowest cytotoxicity was observed for NMP: 40 mM. However, as the succindiamides are poorly soluble once transferred to the aqueous cell culture medium, this relatively low observed cytotoxicity could be an underestimation: if only 10% of the succindiamides was in solution, the concentration able to activate the cellular assays was in reality even 10x lower than the reported values in Table 6, corresponding to a 10x higher potency.

The CALUX assays listed in Table 6 detect the ability of a test compound to modulate activation of a certain nuclear receptor (PXR through PPARγ), or a cell signaling pathway (TCF through p53). Since these early molecular events are often involved in multiple adverse outcome pathways, it is not always straightforward to link each assay to a specific toxicological endpoint. Nonetheless, when focusing on the CMR endpoints that are prioritized in REACH legislation, several molecular targets have been shown to be relevant for these endpoints.

The PXR CALUX is a xenobiotic sensor; the fact that compounds activate this assay indicates that they are recognized as non-endogenous to the cells. PXR activation leads to the induction of metabolic enzymes, resulting in enhanced metabolism of a wide range of compounds. Its activation has been correlated with a protective effect against reproductive toxicity.[71] The CALUX results show that NBP activated PXR, while NMP was negative. This is in line with the fact that NMP is a known reprotoxicant, whereas NBP has been tested negative on reproductive toxicity.[28] The three succindiamides were all able to activate PXR, which may indicate that these chemicals are less likely to induce reproductive toxicity.

No activity was observed on the endocrine assays, which measure activation of nuclear hormone receptors (estrogen, androgen, progesterone, glucocorticoid and thyroid) and are often involved in reproductive toxicity.[71] Other receptors that may be relevant in reproductive toxicity, like PPARs (Martin et al) and AhR, were activated by NMP only (AhR) or NMP and NBP (PPARδ).

Six of the CALUX assays (TCF through p53) detect activation of several cellular signaling pathways, which are indicative of general stress and acute toxicity, but also a range of more specific types of toxicity, including reproductive toxicity. NMP activates three of these assays, which can be linked to reproductive toxicity

Table 6. CALUX assay results presented as lowest effect concentrations (LECs) in Log M.

Test	NMP	NBP	MBSA	EBSA	TBSA
Cytotoxicity	-1.4	-2.1	-2.3	-3.1	-3.4
PXR	-	-3.2	-3.9	-5.0	-6.1
ERα	-	-	-	-	-
AR-anti	-	-	-	-	-
PR-anti	-	-	-	-	-
GR-anti	-	-	-	-	-
TRβ	-	-	-	-	-
TRβ-anti	-	-	-	-	-
AhR	-2.0	-	-	-	-
PPARα	-	-	-	-	-
PPARδ	-2.2	-2.3	-	-	-
PPARγ	-	-	-	-	-
TCF	-2.1	-	-	-	-
AP1	-1.5	-	-	-	-
ESRE	-	-	-2.4	-	-
Nrf2	-	-	-2.9	-	-
p21	-2.0	-	-	-	-
p53	-	-	-	-	-

(-) = no effect observed up to the highest test concentration.

(Wnt signaling (TCF)),[72] cell cycle control (AP-1) or DNA damage response (p21).[73] NBP did not activate any of these assays. Of the succindiamides, only MBSA showed activity on two of the cellular signaling pathway assays: ESRE (unfolded protein response) and Nrf2 (oxidative stress).

Overall, the in vitro analysis showed that the succindiamides activate fewer assays than NMP, but generally at much lower concentrations, suggesting a higher potency. For NMP the LECs are 3-40 mM; for MBSA 0.1-5.0 mM, for EBSA 0.01-0.80 mM and for TBSA even 0.001-0.400 mM. The assays activated by the succindiamides do not show obvious indications for reproductive toxicity. On the contrary: PXR activation, observed for all three succindiamides, has been shown to be inversely correlated with reproductive toxicity;[71] as such, the PXR activation at micromolar concentrations by EBSA and TBSA could be a favourable characteristic.

When comparing the succindiamides to each other, two opposing trends are observed. The number of active assays decreases with increasing chain length (MBSA (4) > EBSA (2) = TBSA (2)), while the potency increases with increasing chain length (LOECs MBSA 0.1-5.0 mM; EBSA 0.01-0.80 mM; TBSA 0.001-0.400 mM).

Conclusion

Amide solvents have received negative publicity in recent years due to their toxicity, with DMF, NMP and DMAc are classed as substances of very high concern (SVHV) by REACH due to their reprotoxicity. The target of this work was to find non-reprotoxic but highly dipolar bio-based or bio-derivable molecules to replace traditional dipolar aprotic solvents. A set of molecules with *N*-butylamide functionality was identified as being a likely route to this objective due to the presence of two amide groups (high dipolarity) with *N*-butyl alkyl chains (low reprotoxicity). Three succindiamide solvents were synthesized, *N*,*N*,*N*',*N*'-tetrabutylsuccindiamide (TBSA), *N*,*N*'-diethyl-*N*,*N*'-dibutylsuccindiamide (EBSA) and *N*,*N*'-dimethyl-*N*,*N*'-dibutylsuccindiamide (MBSA). All are produced from the bio-based platform molecule succinic acid and alkylbutylamines. To produce 100% bio-based solvents, the alkylbutylamines can be synthesized from bio-butanol and a bio-based version of methanol or ethanol.

The succindiamides displayed some unusual properties. Interestingly, all three were immiscible with water but miscible with the non-polar hexane, which is highly uncommon for a dipolar aprotic solvent. The solvents were trialled in the dissolution of industrially relevant polymers (PAI, PVDF and PES) which currently rely on NMP, DMF or DMAc in a number of applications. All three were shown to dissolve high molecular weight PVDF and PAI at elevated temperatures, while MBSA can also dissolve PES for the fabrication of an industrially relevant membrane. Future work should look at utilizing these solvents in applications such as Li battery binders, wire enameling and as co-solvents in membrane formation.

Additionally, a model Heck reaction and two MOF syntheses were carried out, in which comparable performances to traditional solvents were observed when using the succindiamides. An effect of the water immiscibility was observed in the Heck reaction: the ammonium salt produced as a by-product precipitated out of solution, benefitting product isolation.

The toxicity of the succindiamides was assessed using an integrated approach consisting of in silico analysis based on available experimental information, prediction model outcomes and read across data, combined with a panel of in vitro reporter gene assays covering a broad range of toxicological endpoints. Assessment of the in silico predictions and data resulted in none of the succindiamides being likely to exhibit CMRS properties. In addition, the in vitro tests suggested no alarming indications of toxicity, and their activation profile compares favorably to that of NMP, but the analysis should be regarded with some caution because of the poor water miscibility of the compounds.

Overall, despite not possessing as high dipolarity as targeted from the outset of this work, TBSA, EBSA and MBSA performed well in several applications including some common synthetic reactions and solubility tests. They can claim to be green in several criteria, being produced catalytically from biomass, and compare favorably to NMP based on in silico and in vitro toxicity testing which showed no obvious indications of CMRS activity. Finally, the observed unusual water immiscibility makes them interesting candidates for further research in a variety of applications.

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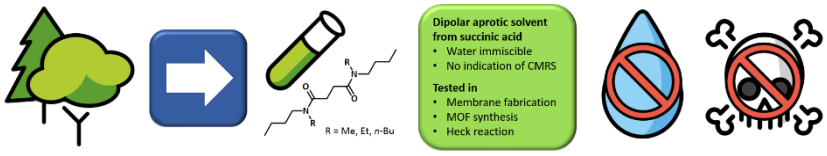

Water immiscible, dipolar aprotic diamide solvents: Three new dipolar aprotic solvents have been synthesized catalytically from succinic acid. Interestingly, all were water immiscible, an unusual property for dipolar aprotic solvents. Tested in a Heck reaction, MOF synthesis and membrane fabrication, they perform comparably to traditional dipolar aprotic solvents such as NMP. In vitro and in silico toxicity testing shows no indications of CMRS.

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