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CRITICAL REVIEW

Low melting mixtures in organic synthesis – an alternative to ionic liquids?

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There is a pressing need to replace hazardous and harmful solvents with “green” or “sustainable” media. Natural compounds have recently been used to produce deep eutectic solvents, sugar melts, or ionic liquids. This review presents physicochemical data of these reaction media and highlights recent advances in their use in organic synthesis and biotransformations.

Introduction

What makes a solvent green? The prevalent opinion is that the ideal green solvent is safe for both the human beings and the environment and its use and manufacture are sustainable.^{1,2}

Ionic liquids (ILs) are an intensively investigated class of alternative reaction media. They are defined as salts with a melting point below the boiling temperature of water (100 °C).³ From all of their exceptional properties like low flammability, stability against air and moisture, excellent solvation potential, low water content, chemical and thermal stability, high heat capacity, density and conductivity, their negligibly low vapour pressure is the most prominent feature why they are considered as green. However, one property still in question – their impact on the environment – is intensively discussed.^{4,5} Ideally, the components of a green solvent exhibit low acute toxicity and are rapidly degraded in the environment. The current consensus is that ionic liquids cannot be generalised as either green or toxic,

but that their environmental impact is strongly dependent on the kind of cation and anion used to produce the IL.⁵ For this reason, reaction media entirely composed of biomaterials have been developed which unite the outstanding physicochemical properties of ILs with the advantage of biodegradable and non-toxic starting materials. Additional advantages over ILs are their facile preparation and the use of readily available and inexpensive starting materials.

This review will focus on the application of these solvents made from renewable resources in organic syntheses. Some examples of biotransformations will be portrayed and also the physicochemical properties will be highlighted. As this is a fast growing and widespread field, we are not trying to be comprehensive, but trying to give a general trend of this research area.

Classification of low melting mixtures and their synthesis

A central role in the class of “bio-based” solvents is played by (2-hydroxyethyl)trimethylammonium chloride, or simply choline chloride (ChCl). The quaternary ammonium salt choline is considered as a member of the vitamin B family, supports a

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Carolin Ruß

Carolin Ruß studied chemistry at the University of Erlangen-Nuremberg and at the University of Regensburg. She received her diploma in medicinal chemistry in 2008. In 2012, she received her PhD degree in the working group of Prof. Dr Burkhard König at the University of Regensburg. Her research topic was the conversion of carbohydrates in low melting mixtures.



Burkhard König

Burkhard König received his doctorate in 1991 from the University of Hamburg and continued his scientific education as a postdoctoral fellow with Prof. M. A. Bennett, Canberra, and Prof. B. M. Trost, Stanford. In 1996 he obtained his “Habilitation” at the University of Braunschweig. Since 1999 he has been full professor of organic chemistry at the University of Regensburg. His research interests focus on intermolecular interactions and their use in catalysis, chemosensors or new reaction media.

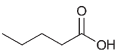
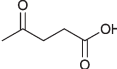
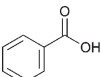
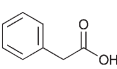
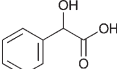
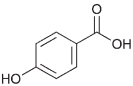
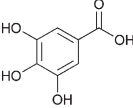
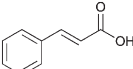
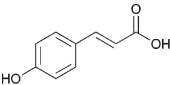
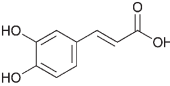
multitude of metabolic processes, and serves as a dietary supplement of animal feeds.⁶ It is commercially produced by a simple gas phase reaction between trimethylamine, ethyleneoxide, and HCl.⁶

The foundation for solvents based on renewable resources was laid in 2003 when Abbott *et al.* reported on low melting mixtures of urea and ChCl which are liquid at room temperature, terming them “deep eutectic solvents” (DESs).⁷ A DES is defined as a mixture of hydrogen bond donor (HBD) systems with simple halide salts which produce liquids.⁸ Their physico-chemical properties resemble those of ionic liquids. Abbott’s fundamental work inspired other researchers to exploit the unusual properties of this system. In the last few years, different (uncharged) hydrogen bond donors of natural and synthetic origin were used in combination with choline chloride.^{8–12} As in the case of ILs, the melting point of the mixtures is not predictable, but some general trends can be derived. Abbott hypothesised that the melting point depression is caused by charge delocalisation due to hydrogen bonding between the halide anion and the hydrogen bond donor.⁷ In ionic liquids, the melting point is dependent on the charge distribution in the ions: the melting points tend to be lower when the charge is strongly delocalised or when the cations and/or anions are asymmetrical.³ A similar effect was observed for melts with quaternary

ammonium salts: with increasing asymmetry of the cation, the melting point decreases.⁷ Furthermore, the freezing points are influenced by the hydrogen bond strength of the different negatively charged counterions of the choline salts in urea mixtures.⁷ The preparation of deep eutectic solvents is very simple: the mixed components are stirred under heating (~80 °C) until a homogeneous, clear liquid has been formed.^{8,12} A subtype of DES are metal-based eutectics made from metal salts like ZnCl₂, FeCl₃, SnCl₂, AlCl₃, and simple organic alcohols or amides as HBDs.^{13,14} The donor molecule serves as a complexing agent and coordinates to the cation.

The exchange of the halide anion for organic anions like carboxylates was a recent advancement to obtain ionic liquids based completely on biomaterials. This concept was firstly introduced by Nockemann *et al.* in 2007.¹⁵ They synthesised ionic liquids by a metathesis reaction of choline chloride and the sodium salts of the non-nutritive artificial sweeteners acesulfame and saccharin, followed by purification using ion-exchange chromatography. Also in 2007, Fukaya *et al.* developed room temperature ionic liquids composed of biomaterials, and termed them “bio ionic liquids”.¹⁶ These so-called “bio-ILs” were prepared by two-step anion exchange reactions of choline hydroxide with different carboxylates. Simple alkanolic acids were used as counterions by Petkovic *et al.* in 2009.¹⁷ They prepared ionic

Table 1 Deep eutectic solvents based on choline chloride (ChCl) and monocarboxylic acids

Entry	Compound	Structure	ChCl : HBD ratio	T_f	T (°C)	Ref.
1	Valeric acid		1 : 2	T_f	22	24
2	Levulinic acid		1 : 2	T_m	Liquid at rt	12
3	Benzoic acid		1 : 2	T_f	95	9
4	Phenylacetic acid		1 : 2	T_f	25	9
5	Mandelic acid		1 : 2	T_f	33	24
6	4-Hydroxybenzoic acid		2 : 1 1 : 2	T_m T_f	87 97	12 24
7	Gallic acid		2 : 1	T_m	77	12
8	<i>trans</i> -Cinnamic acid		1 : 1	T_m T_f	93 101	12 24
9	<i>p</i> -Coumaric acid		2 : 1	T_m	67	12
10	Caffeic acid		2 : 1	T_m	67	12

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

liquids by titration of cholinium hydrogen carbonate with the corresponding acid. Recently, Liu *et al.* introduced room temperature ionic liquids using amino acids as anions and choline as a cation.¹⁸ They also used choline hydroxide as starting material which was added dropwise to an aqueous solution of eighteen different amino acids.


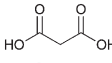
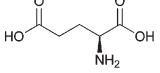
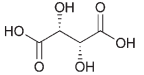
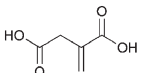
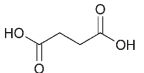
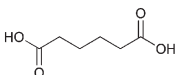
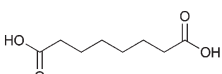
Sugar melts, low melting eutectic mixtures of sugar, urea, and salt were described by Imperato *et al.*^{19–21} The stable melts, which consist merely of neutral components, are prepared by heating up the ground compounds until a clear liquid has formed. The obtained eutectic mixtures exhibit melting points above 60 °C. Even simpler eutectic mixtures termed “natural deep eutectic solvents” (NADES) were published by Choi *et al.* in 2011.²² They presented 30 defined combinations of ChCl, organic acids, amino acids and sugars giving viscous liquids at room temperature. These media might play a role as water-free natural ionic liquids in cells, *e.g.* for dissolving metabolites or as solvents for biochemical reactions.

1 Overview of the physicochemical properties

1.1 Used components and melting points

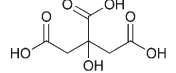
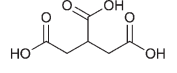
Similar to ILs, the melting points of eutectic mixtures are not yet predictable. The liquid character of the salt mixtures is attributed to a reduction of Coulomb forces. They decrease with a large volume (or buried charge) and asymmetric charge distribution of the molecular ions. The melting points (T_m), freezing points (T_f) or glass transition temperatures (T_g) are summarised below (Tables 1–10). In those cases, when two different melting points were determined, both values are given. Interestingly, the melting points of DESs and ILs made from the same components, *e.g.* benzoic acid (Table 1, entry 3) and benzoate (Table 8, entry 17) or tartaric acid (Table 2, entry 4) and H-tartrate (Table 8, entry 16), deviate strongly from each other; mostly, the melting points of the DESs are lower than the melting points of the ILs. The temperature stability of the eutectic mixtures is also lower compared to the ILs. For example, urea

Table 2 Deep eutectic solvents based on choline chloride and dicarboxylic acids

Entry	Compound	Structure	ChCl : HBD ratio	T (°C)	Ref.	
1	Oxalic acid		1 : 1	T_f	34	9
2	Malonic acid		1 : 1	T_f	10	9
3	Glutamic acid		1 : 2	T_f	13	24
4	L-(+) Tartaric acid		2 : 1	T_m	47	12
5	Itaconic acid		1 : 1 2 : 1	T_m	57	12
6	Succinic acid		1 : 1	T_f	71	9
7	Adipic acid		1 : 1	T_f	85	9
8	Suberic acid		1 : 1	T_m	93	12

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

Table 3 Deep eutectic solvents based on choline chloride and tricarboxylic acids

Entry	Compound	Structure	ChCl : HBD ratio	T_f (°C)	Ref.
1	Citric acid		2 : 1	69	9
2	Tricarballic acid		2 : 1	90	9

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

Table 4 Deep eutectic solvents based on choline chloride and alcohols

Entry	Compound	Structure	ChCl : HBD ratio	T_f (°C)	Ref.	
1	Glycerol		1 : 2	T_f	−40	8
2	Ethylene glycol		1 : 2	T_f	−20	24
3	Mannitol		1 : 1	T_f	108	24
4	D-Fructose		1 : 2	T_f	5	24
5	D-Glucose		1 : 2	T_f	14	24
6	Vanilline		1 : 2	T_f	17	24
7	Xylitol		1 : 1	T_m	Liquid at rt	12
8	D-Sorbitol		1 : 1	T_m	Liquid at rt	12
9	D-Isosorbide		1 : 2	T_m	Liquid at rt	12

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

Table 5 Deep eutectic solvents based on choline chloride and urea derivatives

Entry	Compound	Structure	ChCl : HBD ratio	T_f (°C)	Ref.
1	Urea		1 : 2	12	7
2	1,3-Dimethylurea (DMU)		1 : 2	70	7

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

Table 6 Other natural ammonium salts used in eutectic mixtures

Entry	Ammonium salt (AS)	Structure	HBD	Ratio (AS : HBD)	T_m (°C)	Ref.
1	L-Carnitine		Urea	2 : 3 (wt : wt)	74	25
2	Betaine hydrochloride		Urea	15 : 85 (mol : mol)	27	26
3	Betaine hydrochloride		Glycerol		rt	27

Table 7 Some eutectics based on metals and donor molecules

Entry	HBD	Metal salt	Ratio (HBD : salt)	T_f (°C)	Ref.
1	Urea	ZnCl ₂	7 : 2	9	13
2	Ethylene glycol	ZnCl ₂	4 : 1	−30	13
3	ChCl	ZnBr ₂	1 : 2	38	28
4	ChCl	FeCl ₃	1 : 2	65	28
5	ChCl	SnCl ₂	1 : 2	37	28

Table 8 Ionic liquids based on the cholinium cation and carboxylates (entries 1–17) and artificial sweeteners (entries 18 and 19)

Entry	Compound	Structure	T_m (°C)	T_g (°C)	Ref.
1	Acetate		51 80	n.d. ^a n.d. ^a	16 17
2	Propionate		n.d. ^a	-74	16,17
3	Butanoate		45		17
4	Valeric acid		31		17
5	Hexanoate		52		17
6	Octanoate		26		17
7	Decanoate		50		17
8	Isobutyrate		35		17
9	Pivalate		57		17
10	Glycolate		38	-67	16
11	Tiglate		n.d. ^a	-62	16
12	H-Succinate		n.d. ^a	-52	16
13	H-Maleate		25	-72	16
14	H-Fumarate		80	n.d. ^a	16
15	H-Malate		99	-40	16
16	H-Tartrate		131	-6	16
17	Benzoate		47	-51	16
18	Acesulfamate		69	n.d. ^a	15
19	Saccharinate		25	n.d. ^a	15

Expectedly, the molar ratio of anions to cations is 1 : 1. ^a n.d. not detected.

decomposes at 210 °C in ChCl–urea DES;²³ sugars usually decompose at about 150 °C, and the most stable Bio-IL, [Ch]-[H-maleate], has a decomposition temperature of 223 °C.¹⁶

1.1.1 Deep eutectic solvents based on choline chloride. See Tables 1–7.

1.1.2 Ionic liquids using choline as a cation and natural products as counterions. See Tables 8 and 9.

1.1.3 Low melting sugar mixtures. See Table 10.

Table 9 Ionic liquids based on the cholinium cation and amino acids as counterions (molar ratio 1 : 1)

Entry	Counterion	T_g (°C)	Ref.	Entry	Counterion	T_g (°C)	Ref.
1	Glycine	-61	18	Empty	Tryptophan	-12	18
2	Alanine	-56	18	10	Proline	-44	18
3	Serine	-55	18	11	Aspartic acid	-22	18
4	Threonine	-39	18	12	Glutamic acid	-18	18
5	Valine	-74	18	13	Asparagine	-14	18
6	Leucine	-47	18	14	Glutamine	-40	18
7	Isoleucine	-47	18	15	Lysine	-48	18
8	Methionine	-61	18	16	Histidine	-40	18
9	Phenylalanine	-60	18	17	Arginine	-10	18
				18			

1.2 Polarity

Solvent polarity is an important factor in chemistry as it can significantly influence the course of the reaction.³⁰ Different scales exist to estimate the polarity of a solvent. One of the most commonly used empirical polarity scales is the $E_T(30)$ scale, introduced by Reichardt.³¹ The polarity is calculated from the wavelength (nm) of maximum absorbance of the standard solvatochromic betaine dye no. 30 (Reichardt's dye) in solvents of different polarity at room temperature (25 °C) and normal pressure (1 bar) using eqn (1). As $E_T(30)$ is rather sensitive to hydrogen bonding solvents, Nile red or $E_T(33)$ are used instead.³¹ Nile red data are here reported as $E_T(NR)$, calculated from eqn (2).

$$E_T(30)/\text{kcal mol}^{-1} = hc\nu_{\text{max}}N_A = 28\,591/\lambda_{\text{max},30} \quad (1)$$

$$E_T(NR)/\text{kcal mol}^{-1} = hc\nu_{\text{max}}N_A = 28\,591/\lambda_{\text{max},NR} \quad (2)$$

(h = Planck's constant, c = speed of light, ν_{max} = wave number of absorption maximum, N_A = Avogadro's constant)

A normalised scale (E_T^N) was introduced to obtain dimensionless values, using water ($E_T^N = 1.00$) and tetramethylsilane ($E_T^N = 0.00$) as reference solvents, resulting in eqn (3).

$$E_T^N = \frac{[E_T(\text{solvent}) - E_T(\text{TMS})]}{[E_T(\text{water}) - E_T(\text{TMS})]} \quad (3)$$

Table 11 summarises $E_T(30)$, E_T^N , and $E_T(NR)$ values of some common molecular solvents, ILs, sugar melts, and DES.

The polarities of the sugar melts ($E_T(NR) = 50$ – 52) and the DES ($E_T^N = 0.80$ – 0.86) are comparable to those of short chain alcohols (e.g. ethylene glycol, 2-propanol) and other polar, aprotic solvents (e.g. DMSO, DMF) ($E_T(NR) = 51$ – 53 kcal mol⁻¹, $E_T^N = 0.39$ – 0.81), and follow a similar trend to common ionic liquids.³⁴

1.3 Viscosity

Viscosity describes the internal friction of a moving fluid or, in other words, the resistance of a substance to flow. Usually, the dynamic viscosities η for ILs are reported in centipoise (cP) which corresponds to milli Pascal-second (mPa s) in SI units. While viscosities of ILs range from around 10 cP to values beyond 500 cP,³ the viscosities of the low melting mixtures, shown in Table 12, range from 50 to 5000 cP for the mixtures of choline chloride with carboxylic acids,⁹ from 650 to 8500 cP for the ionic liquids of choline with carboxylates,¹⁶ and from 121 to 5640 cP for choline–amino acid liquids and are higher than those of ILs.¹⁸ In comparison with the viscosities of different common solvents like dichloromethane (0.413 cP), DMSO

(1.987 cP), ethylene glycol (16.1 cP), and glycerol (934 cP), the viscosity of low melting mixtures is up to three orders of magnitude higher. Viscosity has a remarkable influence on the course of a chemical reaction: high viscosities can decrease the reaction rate in the case of diffusion-controlled chemical reactions. In engineering, low viscosities are preferred as operational costs for e.g. stirring, mixing, and pumping can be reduced in practice.

All listed low melting mixtures display rather high viscosities. As in ionic liquids, the viscosity of the low melting mixtures increases with increasing size or molecular weight of the anion. Furthermore, strong intermolecular interactions promote high viscosities.

1.4 Density

Typical values for the density of ILs range from 1.12 to 2.4 g cm⁻³ and are therefore higher than those of organic solvents and water.³ The values of ILs are comparable to the densities of choline based ionic liquids and deep eutectic solvents (Table 13).

1.5 Molar heat capacities and conductivity

Molar heat capacities C_p of DESs are important to assess their potential for heat transfer applications. They were measured for pure choline chloride melts with urea, ethylene glycol and glycerol in the temperature range from 303.2 to 353.2 K and were determined to be between 181 and 254 J mol⁻¹ K⁻¹.⁴² Furthermore, C_p values increase with increasing temperature and increasing mole fraction of DES. Similar behaviour has previously been observed for other ionic liquids.⁴³

Conductivity σ is the ability of a material to transmit an electric current. It depends on the available charge carriers (ionicity) and their mobility, the valence of the ions, and the temperature. The ionic conductivity of ILs is reduced compared to highly concentrated aqueous electrolytic solutions and amounts to up to 10 mS cm⁻¹. The moderate conductivities might result from a reduced ion mobility due to a large ion size and/or ion pairing or ion aggregation leading to a smaller amount of available charge carriers.³

Table 14 shows the conductivities observed in DESs which are comparable to ionic liquids;^{44,45} DESs are therefore a highly investigated medium for electrochemical applications.^{46–63} Readers interested in electrodeposition from ILs and DESs will find a good review in ref. 64.

2 Reactions in low melting mixtures

Deep eutectic solvents and sweet eutectic mixtures are an environmentally benign alternative to hazardous (organic) solvents and

Table 10 Melting points and composition of low melting sugar mixtures

Entry	Carbohydrate	Structure	Urea	Salt	Ratio ^a	T _m	Ref.
1	Citric acid		DMU	—	40 : 60	65	20
2	Sorbitol		DMU	NH ₄ Cl	70 : 20 : 10	67	20
3	Maltose		DMU	NH ₄ Cl	50 : 40 : 10	84	20
4	Mannitol		DMU	NH ₄ Cl	50 : 40 : 10	89	20
5	Lactose		DMU	NH ₄ Cl	50 : 40 : 10	88	20
6	Mannose		DMU	—	30 : 70	75	20
7	Fructose		DMU	—	40 : 60	80	20
8	Fructose		Urea	NaCl	70 : 20 : 10	73	20
9	Fructose		Urea	—	40 : 60	65	19
10	Glucose		Urea	NaCl	60 : 30 : 10	78	20
11	Glucose		Urea	CaCl ₂	50 : 40 : 10	75	19
12	Glucose			—	50 : 50	75	29
13	Galactose		Urea	NH ₄ Cl	30 : 70 : 10	80	29
14	<i>N</i> -Acetyl-D-glucosamine		Urea	NH ₄ Cl	30 : 70 : 10	80	29
15	L-Rhamnose		Urea	NH ₄ Cl	30 : 70 : 10	80	29
16	2-Deoxy-D-glucose		Urea	NH ₄ Cl	30 : 70 : 10	80	29

DMU: 1,3-dimethylurea.^a Sugar : urea : salt ratio (weight%).

might replace them in part. Their application in organic synthesis has notable advantages. As most of the components are soluble in water, addition of water to the reaction mixture dissolves the

reaction medium. The organic products either form a separate layer or precipitate and can be filtered off. Furthermore, the solvent and the catalyst may be reused for another reaction cycle.

Table 11 Overview of determined $E_T(30)$, E_T^N , and $E_T(NR)$ (for the dye Nile Red) values of some common molecular solvents, ILs, sugar melts, and DES

Solvent	$E_T(30)$ kcal mol ⁻¹	E_T^N	$E_T(NR)$	Ref.
Water	63.1	1.000	48.21	20,31
Glycerol	57.0	0.812	—	31
Ethylene glycol	56.1	0.784	50.6	20
	56.3	0.790	—	31
Ethanol	51.9	0.654	—	31
2-Propanol	48.5	0.549	52.94	20
	48.4	0.546	—	31
Dimethylsulfoxide	45.0	0.441	52.07	20
	45.1	0.444	—	31
Dimethylformamide	43.6	0.398	52.84	20
	43.2	0.386	—	31
[Bmim][acetate]	50.5	0.611	—	32
[Bmim][propionate]	49.1	0.568	—	32
[Bmim][H-maleate]	47.6	0.522	—	32
Citric acid–DMU	70.8	1.238	49.72	20
Sorbitol–DMU–NH ₄ Cl	68.1	1.154	50.16	20
Maltose–DMU–NH ₄ Cl	67.8	1.145	50.60	20
Fructose–urea–NaCl	66.5	1.105	52.55	20
Mannitol–DMU–NH ₄ Cl	65.8	1.083	52.94	20
Glucose–urea–NaCl	64.4	1.040	50.78	20
Lactose–DMU–NH ₄ Cl	53.9	0.716	52.55	20
Mannose–DMU	53.9	0.716	51.79	20
Carnitine–urea	—	—	49.89	25
Glycerol–ChCl	58.58	0.86	—	8
	—	0.84	—	33
Ethylene glycol–ChCl	—	0.80	—	33
Urea–ChCl	—	0.84	—	33

[Emim]: 1-Ethyl-3-methylimidazolium, [Bmim]: 1-butyl-3-methylimidazolium.

2.1 Reactions in DES

A variety of organic reactions were performed in deep eutectic solvents, mainly focused on the choline chloride–urea (1 : 2) eutectic mixture (Fig. 1).

In 2010, high yields and high purities were reported for the bromination of 1-aminoanthra-9,10-quinone with molecular bromine in short reaction times.⁶⁵ Moreover, the reaction time and temperature of the Perkin reaction can be remarkably reduced without the use of a catalyst, while simultaneously improving the yields.⁶⁶ Coumarins were synthesized *via* a Knoevenagel condensation in short reaction times and high yields starting from salicyl aldehydes and active methylene compounds.⁶⁷ Recently, it was shown that the reduction of epoxides and carbonyl compounds with sodium borohydride can be conducted regio- and chemoselectively in good to excellent yields.⁶⁸

2.2 Reactions in low melting (carbohydrate) mixtures

“Sweet” low melting mixtures based on simple sugars or sugar alcohols and urea (derivatives) were introduced as reaction media for a variety of organic C–C-coupling reactions (Fig. 2). The Diels–Alder reaction of cyclopentadiene with methyl acrylate was performed in high yields and *endo/exo* ratios comparable to those using ionic liquids and *sc*CO₂.^{19,69} Metal-catalysed reactions like Suzuki,^{20,25} Heck,²⁵ and Sonogashira reactions,²⁵ and the Huisgen 1,3-dipolar cycloaddition²⁵ were also successfully conducted in high yields. By exchanging the sugar melts

Table 12 Viscosities of some common organic solvents, regular ionic liquids, “bio ILs”, and sugar–urea-melts

Solvent	η (cP) at rt	Ref.
CH ₂ Cl ₂	0.413	35
MeOH	0.544	35
Water	0.890	35
DMSO	1.987	35
Ethylene glycol	16.1	35
Glycerol	934	35
[Ch][maleate]	650	16
[BMmorf][maleate]	11.54	36
[Emim][maleate]	383	16
[Ch][saccharinate]	328 (at 70 °C)	15
[Ch][acesulfamate]	1072	15
[Ch][glu]	2308	18
[Bmim][glu]	83	37
[Ch][gly]	121	18
[Bmim][gly]	67	37
[Emim][gly]	61	38
[Ch][ser]	402	18
[Emim][ser]	411	38
[Ch][pro]	500	18
[Emim][pro]	426	38
Fructose–DMU	35.3	39
Citric acid–DMU	289.6	39
Maltose–DMU–NH ₄ Cl	1732.7	39
Urea–ZnCl ₂	11 340	13
ChCl–ZnCl ₂	85 000	28
Acetamide–AlCl ₃	60	14

Ionic species are enclosed in brackets; amino acids were abbreviated using the three letter code. [Ch]: choline, [Emim]: 1-ethyl-3-methylimidazolium, [Bmim]: 1-butyl-3-methylimidazolium, [BMmorf]: 4-benzyl-4-methylmorpholinium.

Table 13 Densities of different choline based DESs and ILs

Solvent	Molar ratio	Density ρ [g cm ⁻³]	Ref.
[Ch][propionate]	1 : 1	1.23	40
[Ch][tiglate]	1 : 1	1.23	40
[Ch][H-maleate]	1 : 1	1.38	40
[Ch][saccharinate]	1 : 1	1.383	15
[Ch][acesulfamate]	1 : 1	1.284	15
ChCl–urea	1 : 2	1.25	10,41
ChCl–ethylene glycol	1 : 2	1.12	37
ChCl–glycerol	1 : 2	1.18	37
ChCl–malonic acid	1 : 1	1.25	37
Urea–ZnCl ₂	7 : 2	1.63	13
Ethylene glycol–ZnCl ₂	4 : 1	1.45	13
Acetamide–AlCl ₃	1 : 1	1.4	14

Table 14 Conductivity of some DESs and ILs

Solvent system	Conductivity σ (mS cm ⁻¹)	Ref.
ChCl–carboxylic acids	0.1 to 10	9
ChCl–urea	0.199	10
ChCl–ethylene glycol	7.61	11
ChCl–glycerol	1.047	11
Acetamide–AlCl ₃	0.804	14
ChCl or urea – ZnCl ₂	0.18 to 0.06	13
[Ch][saccharinate]	0.21	15
[Ch][acesulfamate]	0.45	15

by a carnitine–urea melt, reduced yields in the Heck reaction, a lower *endo/exo* ratio in the Diels–Alder reaction, but similar yields in the Huisgen 1,3-dipolar cycloaddition were observed.²⁵

Although the melts consist of chiral components, no asymmetric induction was observed in the catalytic hydrogenation of acetamido α -cinnamate.²⁰ Quinazoline derivatives were synthesised in high yields *via* a one-pot three-component coupling reaction of 2-aminoaryl ketones, aldehydes, and ammonium acetate using maltose–DMU–NH₄Cl.⁷⁰

The use of the sweet solutions is still limited due to their relatively high melting points. Another drawback of the melts is that their components are not chemically inert. However, a virtue can be made out of necessity. The reactivity of the sugars was utilised to convert efficiently carbohydrates into different glycosyl ureas.²⁹ Furthermore, 5-hydroxymethylfurfural, an important organic intermediate, was produced in such melts,^{71,72} as well as the glucosylated derivative 5-(α -D-glucosyloxymethyl)furfural (not shown below).⁷³

Inspired by these investigations, low melting mixtures of L-(+)-tartaric acid and urea derivatives were used to synthesise racemic dihydropyrimidinones *via* a Biginelli reaction. Remarkably, the melt fulfils the triple role of being a solvent, a catalyst, and a reactant.⁷⁴

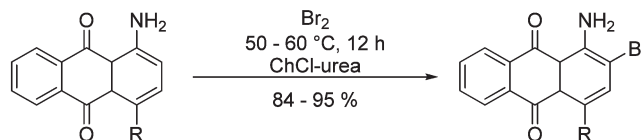
2.3 Biocatalytic reactions

Enzymes catalyse a broad spectrum of organic reactions like hydrolyses, oxidations, reductions, addition–elimination

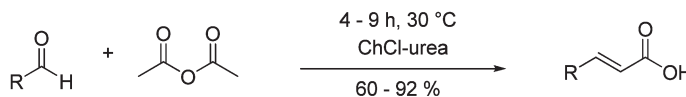
reactions, halogenations, *etc.* chemo-, regio- and enantioselectively.⁷⁵ Their natural medium is water. However, hydrophobic reactants and products are sparingly soluble in water. Although enzymes display the highest catalytic activity in water, the biocatalysts can work in non-aqueous media, such as organic solvents or ionic liquids. The most prominent advantage of non-aqueous media is that thermodynamic equilibria can be shifted from hydrolysis to synthesis. Accordingly, hydrolases can be used to form ester or amide bonds. Furthermore, side reactions, like hydrolysis or protein degradation, which often occur in aqueous solutions, might be suppressed in non-aqueous media. ILs have been applied as non-aqueous media in biotransformations and the field has recently been summarised in several reviews.^{76–78} Enzymes generally show comparable or higher activities in ionic liquids than in conventional organic solvents and in some cases, they also exhibit enhanced thermal and operational stabilities and give higher regio- or enantioselectivities.⁷⁷ It is believed that enzymes can retain a residual hydration shell in non-polar solvents which stabilises the native fold.⁷⁹

Due to their similar physicochemical properties, it was thus evident to investigate deep eutectic solvents as reaction media for biotransformations. Gorke *et al.* were the first to use enzymes in DESs and to assess the activity of different hydrolases in choline chloride–urea mixtures.³³ Despite high concentrations of urea, which is a strong hydrogen bond donor and denatures proteins, and the presence of halides, which might inactivate or

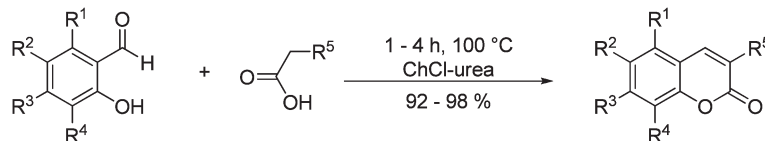
Bromination⁶⁵



Perkin reaction⁶⁶



Knoevenagel condensation⁶⁷



Reduction of epoxides and carbonyl compounds⁶⁸

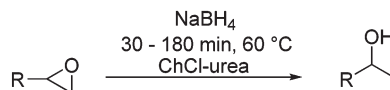
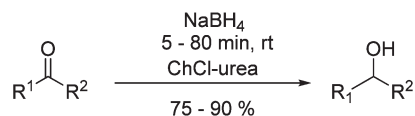
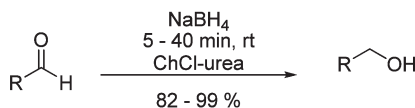


Fig. 1 Some organic reactions in DESs (choline chloride (ChCl)–urea mixtures).

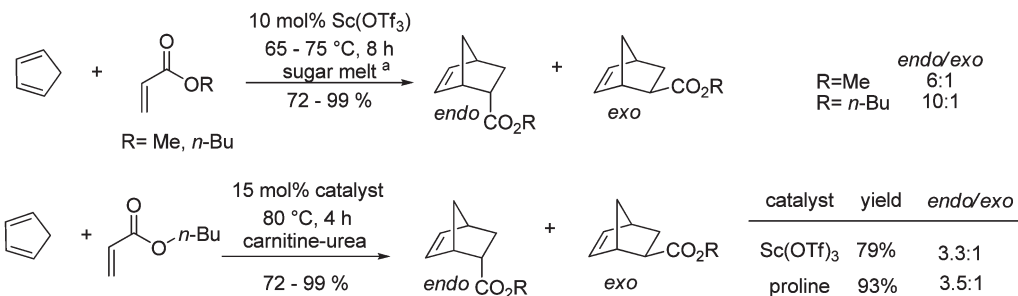
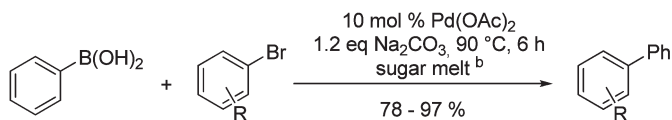
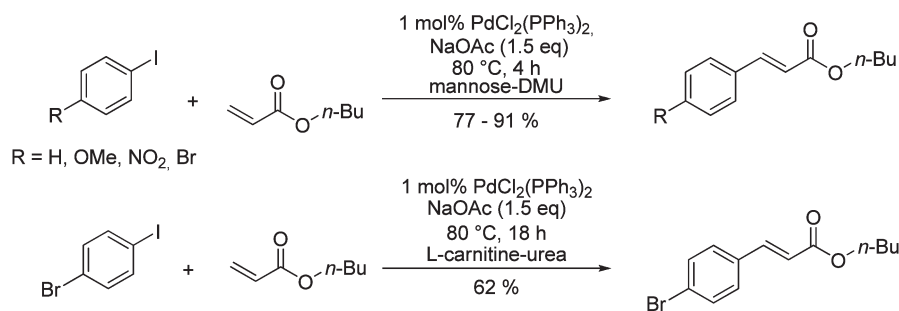
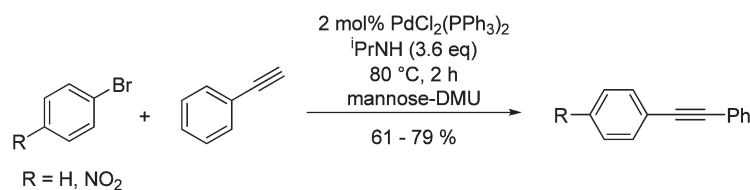
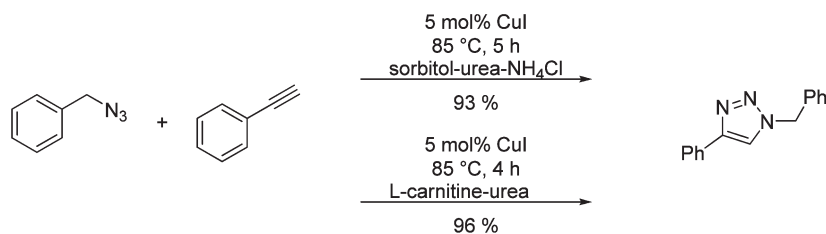
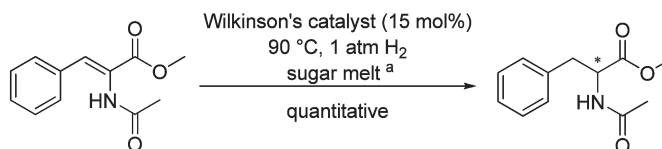
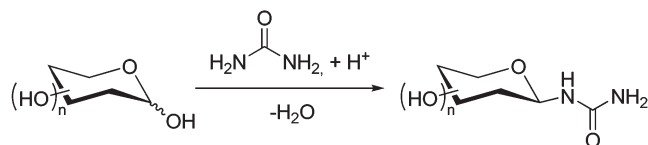
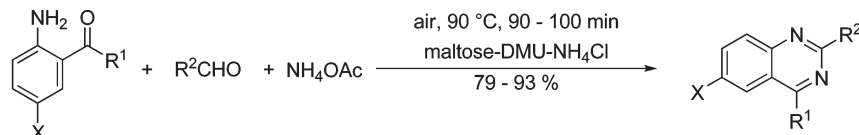
Diels-Alder^{19, 25}Suzuki coupling²⁰Heck reaction²⁵Sonogashira reaction²⁵Huisgen 1,3 dipolar reaction²⁵Catalytic hydrogenation²⁰

Fig. 2a

Synthesis of glycosylureas²⁹



Catalyst free quinazoline multicomponent synthesis⁷⁰



Biginelli reaction⁷⁴

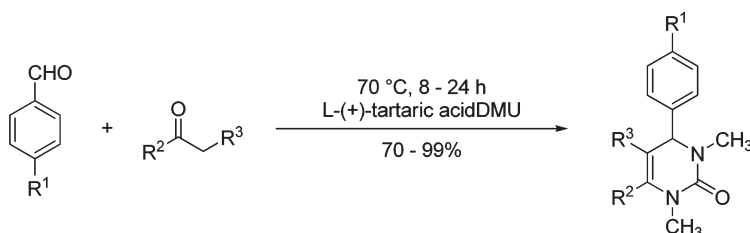
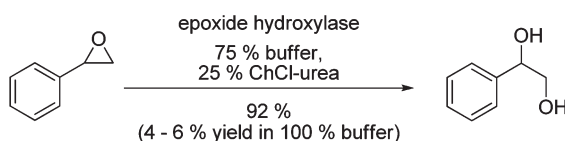


Fig. 2b Organic reactions in low melting carbohydrate mixtures. ^aCarbohydrate melts used as reaction media: fructose–DMU (7 : 3), maltose–DMU–NH₄Cl (5 : 4 : 1), lactose–DMU–NH₄Cl (6 : 3 : 1), mannitol–DMU–NH₄Cl (5 : 4 : 1), glucose–urea–CaCl₂ (5 : 4 : 1), sorbitol–DMU–NH₄Cl (7 : 2 : 1), citric acid–DMU (4 : 6). ^bCarbohydrate melts used as solvents: fructose–urea–NaCl (7 : 2 : 1), maltose–DMU–NH₄Cl (5 : 4 : 1), mannose–DMU (3 : 7), lactose–DMU–NH₄Cl (6 : 3 : 1), mannitol–DMU–NH₄Cl (5 : 4 : 1), sorbitol–DMU–NH₄Cl (7 : 2 : 1), glucose–urea–NH₄Cl (6 : 3 : 1).

Epoxide hydrolysis³³



Biginelli in DES with lipase⁸³

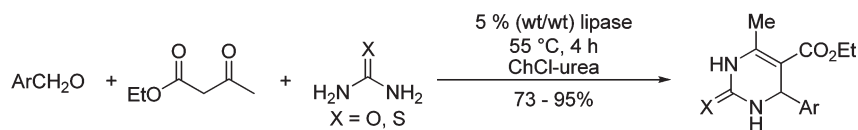


Fig. 3 Some biotransformations in DES.

inhibit the proteins, the enzymes showed good catalytic activity. Furthermore, the conversion of styrene oxide to the corresponding diol with epoxide hydrolase was 20-fold enhanced using choline chloride–urea as a co-solvent (Fig. 3).³³ The hydrolysis of epoxides has been studied in more detail by Lindberg *et al.*⁸⁰ They investigated the effect of different DESs (1 : 2 mixture of ChCl with urea, ethylene glycol, or glycerol) as co-solvents on the hydrolysis of chiral (1,2)-*trans*-2-methylstyrene oxide enantiomers by potato EH StEH1 hydrolase. By applying DESs as co-solvents, higher reactant concentrations could be achieved and the regioselectivity could be influenced. Zhao *et al.* studied the protease-catalysed transesterification activities in choline chloride–glycerol mixtures (1 : 2).⁸¹ *N*-Acetyl-1-phenylalanine

propyl ester was produced from the corresponding ethyl ester in 1-propanol with 98% selectivity and this reaction was favoured over the hydrolysis to the carboxylic acid. The same group developed a new species of the eutectic mixture, a combination of the ionic liquid choline acetate with glycerol as a hydrogen bond donor, thus achieving lower viscosity.⁸² *Candida antarctica* lipase B catalysed highly selectively (>99%) the transesterification of ethyl sorbate with 1-propanol in DES, as well as the transesterification of a mixture of triglycerides with methanol to biodiesel.

The combination of DES and the enzyme lipase from *Rhizopus oryzae* as biocatalyst was used to synthesise (racemic) dihydropyrimidines by a Biginelli reaction (Fig. 3).⁸³

2.4 Other applications

ILs can even dissolve a wide variety of molecules and materials of low solubility. Different deep eutectic solvents (ChCl–urea, ChCl–malonic acid) increase the solubility of poorly soluble compounds (e.g. benzoic acid, griseofulvin, danazol, itraconazole) 5- to 20 000-fold compared to their solubility in water.⁸⁴ In NADES, an enhanced solubility of the flavonoid rutin, which is only slightly soluble in water, was observed.²² The solubility was 50- to 100-fold higher in glucose/fructose or aconitic acid/ChCl mixtures than in water.²²

Deep eutectic solvents are also versatile tools for the synthesis of inorganic materials and play a structure directing role as templates for the framework formation of metal phosphates,⁸⁵ oxalato-phosphates,⁸⁶ aluminophosphates,⁸⁷ carboxymethyl-phosphonates,⁸⁸ oxalato-phosphonates,⁸⁹ polyoxometalate-based hybrids,⁹⁰ zeolites,⁹¹ or metal–organic frameworks.⁹² Their structure directing role was also observed for nucleic acids which can form several secondary structures that reversibly denature on heating in a water-free DES. Four distinct nucleic acid structures can exist in DESs or room-temperature ILs.⁹³

Furthermore, monodispersed concave tetrahedral Pt nanocrystals were prepared by electrochemical shape-controlled synthesis in deep eutectic solvents.⁴⁸ Using this new synthetic method, the size and shape of the nanocrystals can be controlled without addition of seeds, surfactants, or other chemicals.

In addition, ionic liquids derived from choline were also used to dissolve biopolymers. Choline acetate was reported to dissolve approx. 2–6 wt% of microcrystalline cellulose within 5–10 min at 110 °C.⁹⁴ In another example, high solubilities of lignin and xylan were observed in liquids produced from choline and amino acids; they were also used for the selective extraction of lignin from lignocellulose.¹⁸ Cholinium alkanoates were shown to efficiently and specifically dissolve suberin domains from cork biopolymers.⁹⁵

Conclusion and outlook

Referring to the twelve principles of green chemistry, the synthesis of the reported eutectic mixtures is more energy efficient as the raw materials are simply mixed and heated without the need of ion-exchange chromatography and thorough purification. However, the lower temperature stability of the mixtures makes recycling more difficult and reduces the overall efficiency and economy. Additionally, the energy efficiency is lower for the mixtures, which are not liquid at room temperature. The use of ions with a smaller size or ionic radius to reduce the quite high viscosities of the liquids might increase the freezing point at the same time.

In contrast to ILs, DESs are typically composed of naturally occurring, renewable or well-characterised bulk chemicals. Although ILs can also be made renewable resources,⁹⁶ multi-step syntheses can be necessary to obtain the desired cations or anions. More importantly, DESs and low melting mixtures composed of unmodified, non-toxic and non-persistent natural products are exempted from the registration according to the REACH regulations, Annex 5.

So far, only few data exist on the toxicity and biodegradability of the here presented mixtures. Choline saccharinate and choline

acesulfamate were shown to have a very low ecotoxicity in a standard assay with the crustacean *Daphnia magna*.¹⁵ The toxicity evaluation of cholinium alkanoates using filamentous fungi as model eukaryotic organisms proved that fungi can actively grow in media up to concentrations in the molar range.¹⁷ Choline is expected to be non-toxic and biodegradable as it is applied as an additive in human nutrition and as animal feed. Care must be taken using metal-based eutectics. The salt ZnCl₂, for example, has been classified as hazardous to humans and very toxic to aquatic organisms. In general, all used compounds should be innocuous to human health and environment and they should not be persistent or bioaccumulative. Sugars and amino acids, for example, fulfil these requirements and are, in addition, inexpensive and ton-scale available.

The reliable prediction of the physical properties, such as phase behavior, conductivity or viscosity, of low melting mixtures is still difficult. Experimental determination of the molecular structure of the solvents and their description by theoretical models are prerequisites for a better understanding of how the molecular structure of the components and their intermolecular interactions shape the physical properties of the solvents.

The application and characterisation of low melting mixtures, i.e. deep eutectic solvents, sugar–urea–salt mixtures, and ionic liquids from biomaterials, are still in the early stage of development. Since the first publication on DESs in 2003, the number of related articles has been growing nearly exponentially. Even while writing this review, new articles on the physicochemical properties of these alternative media, their application in synthesis, electrochemistry, or the structure directing role of biopolymers have been published, underpinning their importance and great potential. Basically, their properties and the fields of application overlap with those of regular ionic liquids. Their apparent advantage over ionic liquids, however, is their easy access from inexpensive, non-toxic and completely biodegradable and biocompatible materials. Considering the variety of anions and cations nature provides, an enormous range of combinations could be synthesised to produce environmentally benign solvents, with tailor-made properties.

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