Green Solvents

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Low-Transition-Temperature Mixtures (LTTMs): A New Generation of Designer Solvents

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deep-eutectic solvents · green solvents · hydrogen bonds · separation processes · solvent design

A new generation of designer solvents emerged in the last decade as promising green media for multiple applications, including separation processes: the low-transition-temperature mixtures (LTTMs). They can be prepared by mixing natural high-melting-point starting materials, which form a liquid by hydrogen-bond interactions. Among them, deep-eutectic solvents (DESs) were presented as promising alternatives to conventional ionic liquids (ILs). Some limitations of ILs are overcome by LTTMs, which are cheap and easy to prepare from natural and readily available starting materials, biodegradable, and renewable.

1. Introduction

In the last three decades, the concept "green" acquired a new significance in chemistry. The definition of sustainable development and green chemistry changed the way of thinking in process and chemical engineering.[1,2] The twelve new principles of green chemistry were applied to the "newborn" green engineering. In this context, minimizing the environmental impact of solvents used in chemical production became a prior target: the challenge of finding "green solvents as replacements for nongreen solvents of any kind".[3] New approaches were taken toward the use of safer alternatives with more environmentally friendly properties. Examples are the use of "biosolvents" produced from readily available renewable resources, the substitution of volatile organic solvents by supercritical CO_2, and the use of ILs with negligible vapor pressure and no potential emissions to the atmosphere.[4] But for a large-scale, the life-cycle assessment of the process, the accessibility of certain chemicals or materials, and the cost and degree of recoverability of the solvent are the bottlenecks.

A recent editorial in *Organic Process Research and Development*[5] discourages chemists to use solvents that are either known to be toxic, dangerous for large-scale applications, or expensive to dispose as waste. Promising results were introduced in the field of solvent development by using water,[6] glycerol,[7] poly(ethylene glycol),[8] perfluorinated solvents,[9] ethyl lactate,[10] supercritical fluids,[11] or ILs,[12] among others.

In 2003, Abbott and co-workers[13] presented a new type of solvents, which are formed by mixing urea and choline chloride, both solid starting materials with high melting points. Thereby, a new solvent system that consists of natural and renewable starting materials was introduced. These mixtures form a eutectic with a wide liquid range and interesting properties to be used as a solvent. Hydrogen-bonding interactions are the main driving force of this phenomenon. The study on hydrogen-bond donor–acceptor combinations enables tailoring the nature, physical properties, and phase behavior of this new family of designer solvents.

2. Deep-Eutectic Mixtures as Solvents

The term "deep-eutectic solvent" (DES) was coined by Abbott and co-workers in 2003.[13] They were inspired by the idea of forming liquids by mixing two solid starting materials with high melting points. Since then, the number of reports on the use of DESs has significantly increased. The number of publications with the term "deep-eutectic solvent" reached around 200 entries until October 2012 (search in ISI Web of Science).

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The core of the finding by Abbott and co-workers is the interaction of quaternary ammonium salts with urea (melting point 133 °C). The most commonly used salt is (2-hydroxyethyl)trimethylammonium chloride (choline chloride, melting point 302 °C). This combination of solid starting materials produces eutectic mixtures that are liquid at ambient temperature (melting point 12 °C for a molar ratio of 2:1) and have unusual solvent properties.[13,14] However, this idea was not new; eutectic mixtures were known before and, for example, used to lower the melting point of salts by forming metal–halide complexes.[15,16] Additionally, urea was reported to form eutectic mixtures with some halide salts[17] by decreasing the lattice energy, and thus decreasing the freezing point of the system. Different theories were developed for explaining the formation of stable liquids. Some authors supported the idea of cluster formation, while others explained eutectic phenomena as a mechanical mixture of two components.[18,19]

Abbott and co-workers suggested hydrogen-bonding interactions between urea and the chloride ion from the choline salt as the main cause of the deep freezing-point depression of the mixture. A DES would, in principle, be a result of the right combination of a hydrogen-bond donor (HBD) and a hydrogen-bond acceptor (HBA; Figure 1). Self-association of the HBD and HBA then lowers the entropic difference of the phase transition.[20]

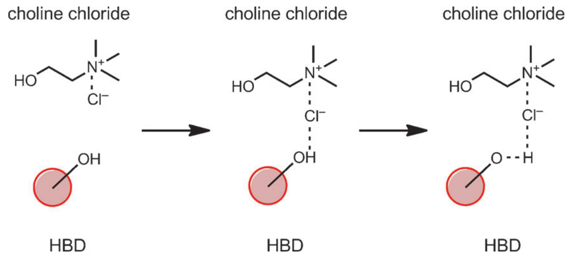

Figure 1. Interaction of a HBD with the quaternary ammonium salt choline chloride.[20]

A large number of different combinations of starting materials shows eutectic behavior. However, the nature of the interactions that take place depends on the type of the counterparts: the "magic" of forming liquids by mixing two or more solid materials. Hydrogen bonds or even van der Waals forces interfere with the ability of the initial compounds to crystallize. Halide salts form DESs by shielding the charge when in the vicinity of certain HBDs. These hydrogen-bonding interactions are reflected in ^{1}H NMR spectra, crystallographic data, or FAB-MS analyses of the mixtures, as reported in previous studies.[21] The strength of the hydrogen bonds can be correlated with the phase-transition temperature, stability, and solvent properties of the respective mixture. In general, the higher the hydrogen-bonding ability of the counterparts (the HBD and the anion of the salt), the deeper the decrease in the freezing point. Therefore, the symmetry of the cation of the salt also influences the trends in the transition temperatures.[13]

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María Francisco received her Chem. Eng. degree at the University of Santiago de Compostela (Spain) in 2006. In 2010, she received her Ph.D. in chemical and environmental engineering and the 2010 EFCE Excellence Award in Thermodynamics and Transport Properties. She joined the Universidad de Las Palmas de Gran Canaria and QUILL at Queen's University of Belfast (UK) under the Marie Curie Early Stage Training Site Fellowship. In 2010, she worked in EBI at the University of Berkeley (California) as a postdoctoral researcher. She is currently a postdoctoral researcher in the group of Separation Technology (TU/e). Her main research interests are applied thermodynamics and separation processes.

Adriaan van den Bruinhorst received his B.Sc. in chemical engineering in 2009 and his M.Sc. in chemical engineering with honors in 2012 at TU/e. His master graduation project titled "Processing Lignocellulosic Biomass with Natural Low Transition Temperature Mixtures (LTTMs)" was awarded by the Taminco Green Footsteps Award 2012 in the field of green solvents. The project was developed in the group of Separation Technology at TU/e, which he joined in September 2012. His main fields of interest are separation processes, green technologies, and reactor engineering.

Since the first paper on DESs was published in 2003, other combinations of DES pairs were explored. In the search for renewable and environmentally friendly solvents, both urea (donor) and choline chloride (acceptor) climbed to the top of the candidates' list as natural and "drinkable" constituents for DESs. The quaternary ammonium salt choline chloride is considered an essential nutrient, which can be extracted from biomass, and is often regarded a part of the B-complex vitamins.[22] Urea plays an important role in the metabolism of nitrogen-containing compounds in mammals and is the most commonly traded nitrogenous fertilizer. Choline cations and related cations, for example betaine cations, can be combined with convenient anions, such as saccharinate, lactate, and hexanoate, to form "drinkable" solvents.[23,24] In 2011, Choi et al.[25] reported the discovery of 30 combinations with choline chloride, natural carboxylic acids, different sugars, and even water, which formed viscous liquids coined "natural deep-eutectic solvents" (NADESs). NADESs are reported to dissolve metabolites in plants. Other authors also prepared new "green" solvents following this strategy.[26,27] New natural LTTMs combining choline chloride, amino acids, different natural carboxylic acids, and other environmentally benign starting materials[28] were also introduced by our group, but the building principles are still not very well understood. The equalization of proton affinity (PA) or pK_a value plays a role in strengthening the hydrogen bond, so the pK_a slide rule can be taken into account in the selection of hydrogen-bonding counterparts.[29] Figure 2 illustrates common examples of HBD and HBA counterparts that can be combined in order to form an LTTM.

Before the mixture of urea and choline chloride was introduced as "deep-eutectic solvent", the reported LTTMs were not named. The versatile character of these combinations for different applications and the lack of standardized literature make it harder to track scientific publications in which any of them are reported. For example, a patent dated from 2002[30] already claimed the possibility of forming numerous eutectic liquids for cosmetic applications. Publications about LTTMs that consist of unconventional components, such as phosponium, imidazolium, or pyridinium salts, are also difficult to trace.[31–33]

The diversity of possible combinations of the starting materials provides a powerful tool to control the physical properties and phase behavior of LTTMs, as well as their ability to dissolve numerous solutes of different nature. Apart from their tunable composition, most LTTMs have other advantageous qualities as solvents. Among them are a wide liquid range, water compatibility, low vapor pressure, nonflammability, biocompatibility, and biodegradability. But one of their most beneficial characteristics is their easy preparation. LTTMs can be formed by simply mixing the starting materials at moderate temperatures with no need of further purification. Many of them can be prepared from cheap, readily available, and toxicologically well characterized starting materials, which also implies low cost.[28] DESs are presented as versatile alternatives to conventional ILs

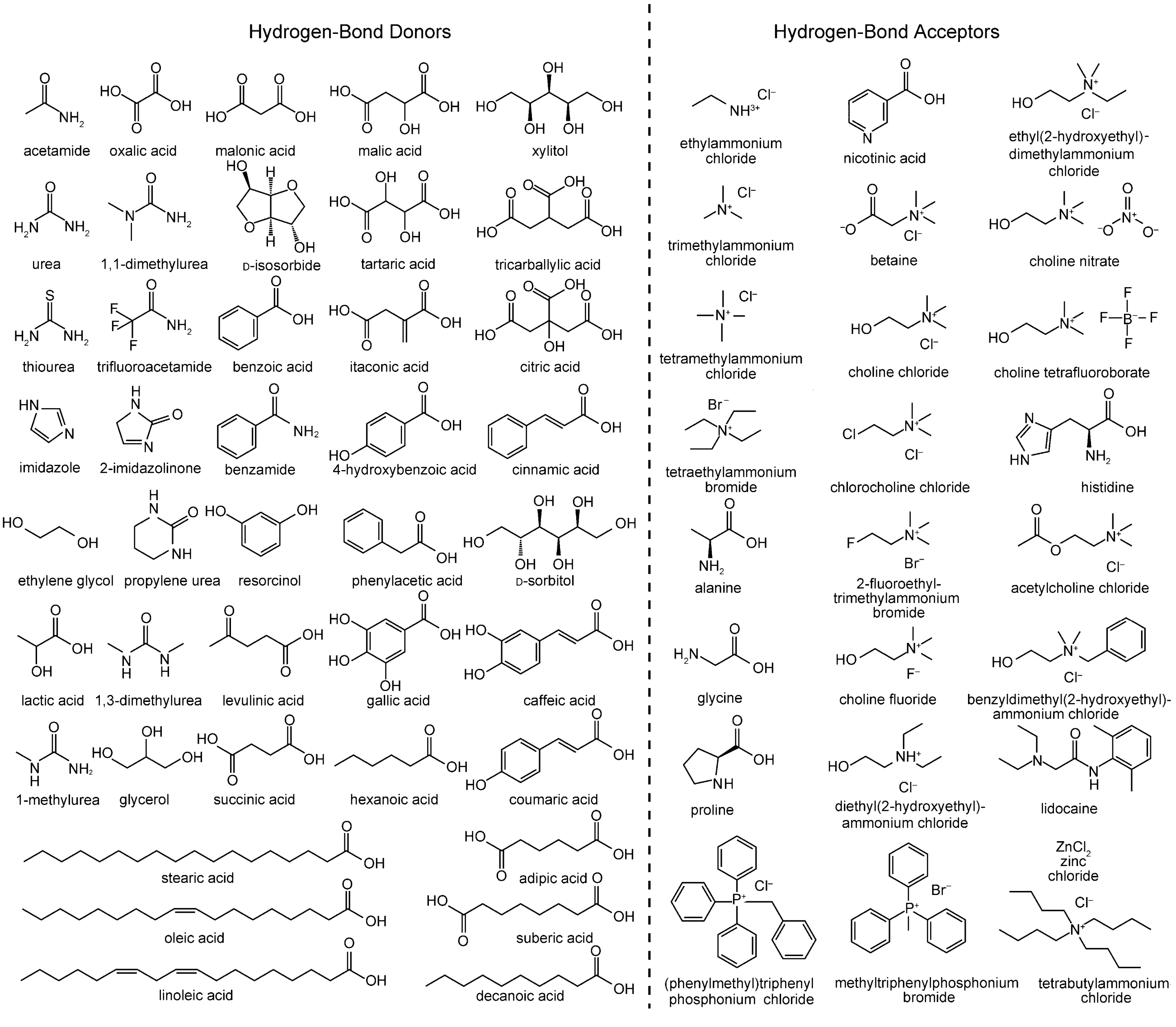


Figure 2. Molecular structures of HBDs and HBAs that can be combined to form a LTTM or a DES.

because they share most of their advantages, but overcome some of their limitations.[34] Additionally, it seems likely that the starting materials of LTTMs are easily recoverable by disrupting or altering complex structures in their matrix. This recoverability can be attributed to the nonexistence of chemical reactions during their formation. In the case of LTTMs, non-hydrogen-bonding solvents are able to interfere with the charge shift of the constituents, inducing nucleation processes to recrystallize the starting compounds. Figure 3 shows an example of liquid mixtures formed in our lab.

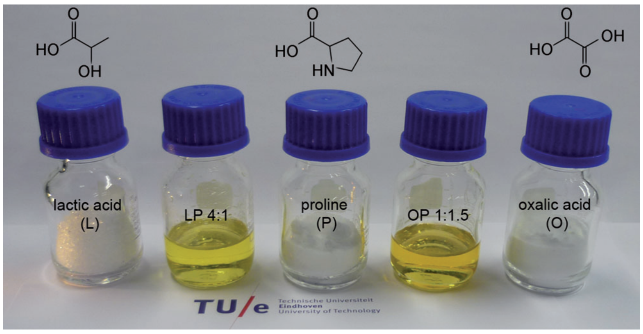


Figure 3. From left to right: lactic acid (solid), lactic acid/proline mixture (liquid), proline (solid), oxalic acid/proline mixture (liquid), and oxalic acid (solid) at room temperature.

3. Physicochemical Properties of LTTMs and DESs as Designer Solvents

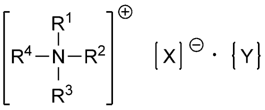
In general, liquid solvents are characterized by several properties that make them more or less suitable as reaction, separation, or heat-transfer media. These properties include physical quantities, such as density, viscosity, liquid range, vapor pressure, refractive index, relative permittivity, and heat capacity. The more "chemical" properties to be discussed include polarity, ability to form hydrogen bonds, and structuredness, among others.[35] The selection criteria for each application are numerous. A trade-off has to be attained between solvent performance, "green character", and economic evaluation of the process. Wouldn't it be a dream to have a magic wand to make all of them possible at the same time?

With a similar idea in mind, but in a different field, a visionary physicist, Richard P. Feynman, challenged the scientific community in the ACS meeting in 1959 by dropping a very simple question: "*What would the properties of materials be if we could really arrange the atoms in the way we want them?*".[36] This is the key of nanotechnology and materials science, but it is also the core of the widespread technology of ILs. K. Seddon described ILs as "designer solvents" by saying: "*In theory at least, ionic liquids can be designed to deliver almost any set of physical and chemical properties for almost any application in the chemical sciences. The solubility and miscibility characteristics of ionic liquids can therefore, in principle, be tailored for specific applications by changing the structure and nature of the cations and/or anions*".[37,38]

DESs are mixtures of HBDs and HBAs, which form liquids with properties comparable to those of ILs. DESs have significant advantages over conventional solvents: their structures can be adjusted by selecting both the nature and the ratio of the hydrogen-bonding constituents, thus allowing an additional degree of freedom. For this reason, all properties are highly influenced by the molar composition of the compounds in the mixture. Temperature, pH value, or water content also have a large effect on the physical and chemical behavior of DESs.

3.1. Effect of Composition

Abbott and co-workers[33] described DESs by the general formula depicted in Figure 4. Because of the huge number of possible variations of the formula (around 10^6 DESs would be in principle possible), they explored the influence of the nature of each of the building elements on the physical properties of the resultant DES. This study is only the top of the iceberg, because a much wider diversity of LTTMs can be formed using different families of salts or even zwitterionic starting materials, such as quaternary phosphonium salts, ILs, or amino acids.



$$\left[\begin{array}{c} R^1 \\ | \\ R^4-N-R^2 \\ | \\ R^3 \end{array}\right]^{\oplus} \; [X]^{\ominus} \cdot \{Y\}$$

Figure 4. General formula of a DES as described by Abbott and coworkers.[33] a) $Y = MCl_x$ with M = Zn, Sn, Fe, Al, Ga; b) $Y = MCl_x \cdot y\,H_2O$ with M = Cr, Co, Cu, Ni, Fe; c) $Y = R^5Z$ with Z = $CONH_2$, COOH, OH.

No correlation was found between the eutectic temperature and the enthalpy of formation of the starting materials. However, it was hypothesized that a relationship exists between the freezing points and the lattice energy of the salt (or HBA), and entropy changes when the liquid is formed.[34] The ratio of constituents at which a eutectic point is found depends on the stoichiometry of the formed complexes. The molar ratios of salt to HBD that result in the mixtures with the lowest melting temperature depend on the nature of both salt and HBD. In a recent review,[39] Zhang et al. concluded that carboxylic acids or sugar-derived polyols are the donors that lead to the lowest freezing point for an acceptor salt. In the case of choline chloride, they form DESs that are liquid at room temperature. The nature of the salt influences the charge shield and thus the strength of the hydrogen bonds. Figure 5 shows some examples of phase-transition temperatures of different combinations of HBDs and HBAs found in the literature.[28,39,40]

Density is a physical property of matter, and of special interest for chemical processing. It changes with the nature and molar ratio of the constituents of DESs. In general, the higher the relative ratio of salt to HBD, the higher the structuring effect on the liquid and the lower the free volume. Lower free volumes imply less molecular motion, and therefore higher viscosities.

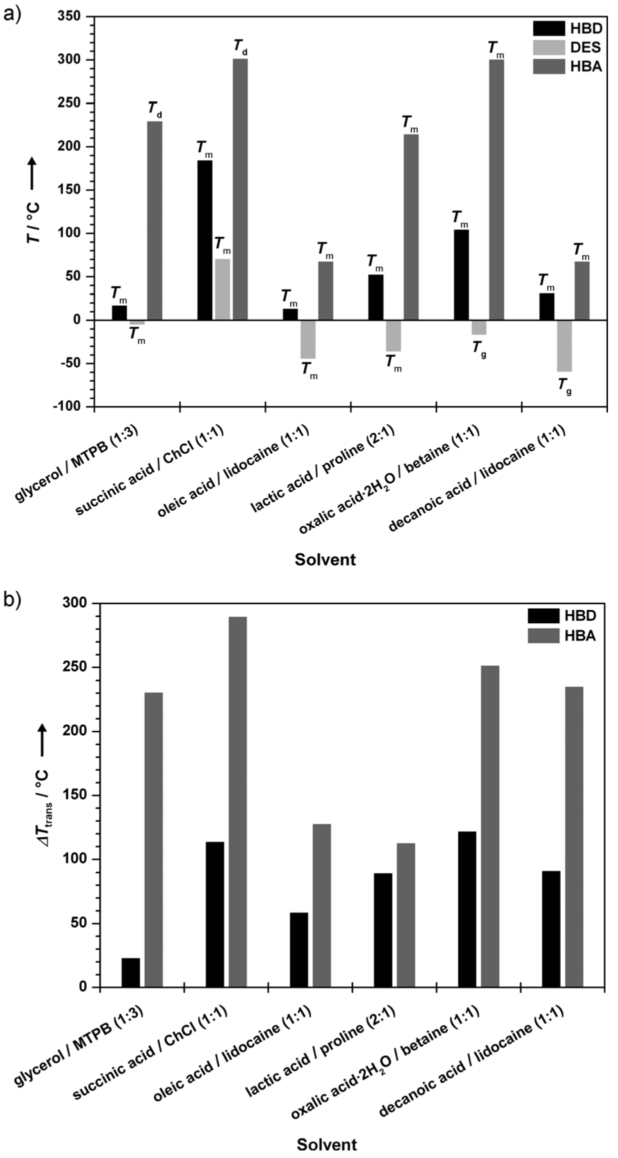


Figure 5. a) Transition temperatures of some representative LTTMs and their constituents; T_d: decomposition, T_g: glass-transition, T_m: melting temperature. b) Difference in transition temperatures (T_{trans}) of some representative LTTMs and their constituents.[28,39,40] MTPB: methyltriphenylphosphonium bromide.

Very recently, the methods developed for the prediction of densities of ILs[41] were successfully applied to the newly formed DESs.[42] These methods enabled the estimation of densities for different families of DESs by combining the concepts of group-contribution methods and artificial neural networks. The Rackett equation modified by Spencer and Danner[43] was employed to predict the density of DESs. Because this strategy uses the modified Lydersen–Joback–Ried method to calculate the critical points, smaller deviations from experimental values were found for DESs with lower molecular weight.

The viscosity of a liquid is a measurement of its intrinsic resistance to flow, reflecting how strong the intermolecular interactions are in this liquid. Recently, the hole theory for liquids was applied to ILs and DESs, and it was observed that they have significantly higher values of viscosity than most molecular solvents and molten salts.[44] This unusual increase in viscosity is also related with the low free volume.[45] Salt that is present in large amounts in the DES system interferes with the intermolecular interactions, generating more free volume and lowering the viscosity. The surface tension follows a similar trend.[44]

3.2. Effect of Temperature

Viscosity, density, surface tension, and conductivity are temperature-dependent properties (see Figures 6 and 7). The molar volume of a liquid solution increases with temperature because higher temperatures imply higher molecular motion. But this change in molecular motion and the deviation from the ideal behavior of liquid mixtures depends on the nature of the involved interactions. The influence of temperature on

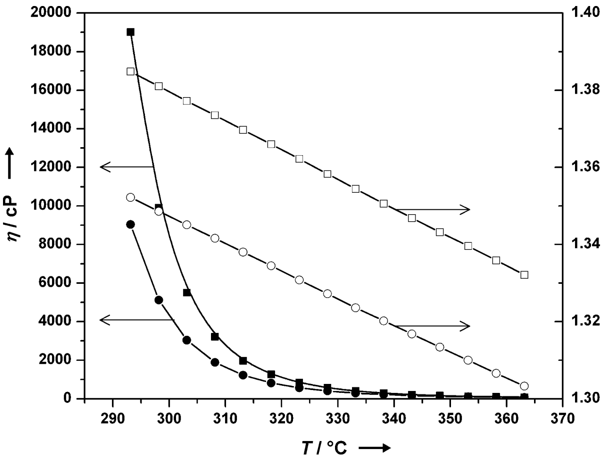


Figure 6. Viscosity (η, solid) and density (ρ, open) of oxalic acid/proline mixtures at molar ratios of 1:1.5 (squares) and 1:1 (circles). Experimental data measured in our group (unpublished results).

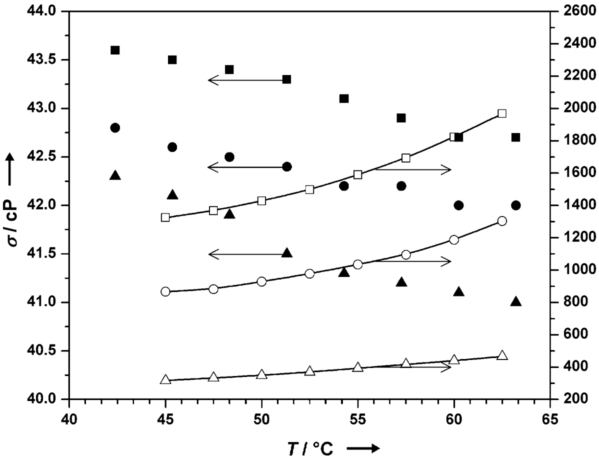


Figure 7. Surface tension (σ, solid) and conductivity (κ, open) as a function of temperature for 1,6-hexanediol/choline chloride (ChCl) mixtures of different compositions (square: 25 %, circle: 15 %, triangle: 5 % ChCl).[20]

density is well-known and understood for most conventional solvents as well as for ILs. A linear dependency of density on temperature is also observed for all reported DESs.[42] Following this line, Kareem et al. showed a linear dependency of refractive index and pH value on temperature for DESs based on phosphonium salts.[31] However, the refractive index depends on electrical permittivity and magnetic permeability. Both properties can change with temperature, but not linearly, and therefore the refractive index does not have a simple relationship with temperature. The changes in other properties, such as conductivity or viscosity, are described using the Arrhenius model or other models such as the Vogel–Tamman–Fulcher (VTF) model.[46]

3.3. *Effect of Water Content*

One of the drawbacks of IL technologies is that, for many applications, a high purity of the solvent is required. ILs are substances that are entirely constituted of ions, so the presence of any kind of ionic or molecular impurity changes their properties to a significant extent. Some of these impurities can even react with water at certain temperatures, resulting in harmful and corrosive by-products (e.g., HF). In real applications, water uptake by the solvent from the surrounding atmosphere is hard to avoid. Therefore, studying the effect of water content on IL properties became a hot research topic.[47]

The superiority of water as solvent can be attributed to many factors. One of these factors is its ability to form hydrogen bonds with a great variety of solutes. LTTMs are formed by mixing two starting materials that are able to form hydrogen bonds. Because of its high polarity, water is one of the few abundant natural substances that act both as donor and acceptor. Hence, water is likely to show strong interactions with the LTTM constituents. The starting materials that are used to prepare LTTMs are likely to be highly hygroscopic. When an LTTM is formed, water is competing with both LTTM constituents for hydrogen bonding. It is thus reasonable to assume that LTTMs are less hygroscopic substances compared to their starting materials. However, this is not always true. In some cases, water interferes with the coordination sphere of the ions, favoring the interactions and entropic state of the final mixture. For this reason, water can form part of the LTTM structure. In fact, it is possible to prepare LTTMs with the hydrated forms of their constituents, such as hydrated salts or acids. This inclusion of water into the structure has the same effect as a change in the composition of the LTTMs. For this reason, hydrated salts or acids do not necessarily form an LTTM in the same range of molar compositions as anhydrous salts or acids. As an example, anhydrous and dihydrated oxalic acid form LTTMs with different HBAs at different ratios.[28] Thus, the liquid range of an LTTM changes upon water addition. Abbott and coworkers proved already in 2004 that hydration of metallic salts is vital for controlling the coordination chemistry around ions.[48a]

When LTTMs are formed without hydrated constituents, it is possible to add water, which can still be enclosed in the intermolecular network, during the preparation. However, this is very difficult to prove. This assumption is based on the fact that after water is added to certain nonhydrated LTTMs, a small amount of it cannot be removed by vacuum distillation. The water is assumed to form part of the solvent itself through stronger intermolecular bonds.

Water has a lower viscosity and density than conventional LTTMs, resulting in a decrease of the values of both properties upon increasing the water content. It was also observed that the impact of water addition varies with the difference in viscosity and density of water and the LTTMs. We observed that upon addition of water, the difference in relative density is much smaller than the decrease in viscosity.[48b]

4. Molecular or Ionic Form: DESs versus ILs

DESs that consist of choline chloride and a HBD have been presented as a versatile alternative to ILs.[34] But … what is behind this idea?

DESs seem to be interesting alternatives to ILs, because they share many of the promising qualities of ILs as solvents, but overcome some of their current drawbacks for large-scale applications, as reported in the previous sections. DESs share one of the most important advantages of ILs as solvents: the ability to customize physical properties and phase behavior by choosing the right constituents with regard to chemical nature, relative compositions, or water content. Compared to ILs, this tailor-made character is even more flexible, because DESs have no strict limitations in terms of stoichiometry. Different to IL synthesis, no reaction takes place during DES preparation, the intermolecular interactions lead to the formation of a liquid within a range of relative molar compositions.[28,49] This means that the physical properties, the ability to dissolve certain solutes, and the phase behavior of DESs can be changed by varying the ratio of its constituents. This feature adds one more degree of freedom to the design of a task-specific solvent.

Like ILs, DESs can be designed to be environmentally benign solvents. However, DESs can be prepared more easily from readily available materials, with high purities, and at lower costs compared to ILs. The preparation of DESs involves only a mixing–heating step and does not require any further purification.

Although DESs share a lot of characteristics with ILs, they are fundamentally different: DESs are mixtures, not ionic compounds. As explained before, the hydrogen-bonding and van der Waals interactions prevent crystallization of the starting materials, thus resulting in the mixtures remaining in liquid state. The strength and nature of the intermolecular forces result in a wide range of different numbers and sizes of holes or empty volumes, which lead to higher or lower mobility of molecules and ions. The nature of these interactions is still electrostatic, which means that the interactions are related to the local charge at the sites of the molecules.

In an interesting communication, Bica et al.[40] reported the liquefaction of a solid pharmaceutical (lidocaine) by mixing it with certain fatty acids. In the search for new IL formulations for anesthetics, the authors observed the formation of a liquid phase out of the solid starting materials as a result of hydrogen bonding. No evidence of proton transfer was found that would result in the expected ionic form. The authors postulated an "*unrecognized state of the proton interaction between the acid and the base*". Based on their broad experience in the field of protic ionic liquids, they ranked the proton interaction/transfer for different classes of mixtures/solvents: immiscible mixtures < eutectics < deep eutectics < partially ionized ILs < fully ionized ILs.

Most of the LTTMs and DESs that were studied until now have an equivalent ionic form which forms an IL. An example is choline lactate (IL) versus lactic acid/choline chloride (LTTM; Figure 8). What is the reason for the IL or the DES form to be present? The selection of the HBD/HBA combination plays the major role. The pK_a values of DES counterparts influence the strength of hydrogen bonds in the mixture, and this behavior has to be taken into account during the selection of the constituents.[29] The acidity of the proton is also responsible for the formation of a molecular LTTM instead of an IL. For instance, when lactic acid is combined with choline chloride, an LTTM is formed at room temperature. The IL choline lactate (under simultaneous formation of HCl) is not produced because HCl is a stronger acid than lactic acid. However, when citric acid is mixed with choline hydroxide, the IL choline citrate (and simultaneously H_2O) is formed instead of the LTTM, because citric acid is a stronger acid than H_2O. For the IL to be formed, a stronger base with a higher pK_a value needs to be combined with the HBD or a stronger acid needs to be combined with the HBA.

Figure 8. Samples of the LTTM lactic acid/choline chloride (2:1; left) and the IL choline lactate (right) at room temperature.

Figure 9 shows the IR spectra of the IL choline lactate versus the LTTM consisting of lactic acid and choline chloride (2:1).[28] The representative peak of the carboxylic acid group of lactic acid (1710 cm^{-1} for the C=O group) can be observed in the LTTM that consists of lactic acid and choline chloride. In the FT-IR spectra of the IL choline lactate, only the representative peak of lactate (1550 cm^{-1} for the C=O group) can be observed. In the LTTM, no evidence of the presence of lactate can be found. Additionally, a shift in ^{1}H NMR signal to lower field was observed for the LTTM, which also reflects the presence of hydrogen-bonding interactions.

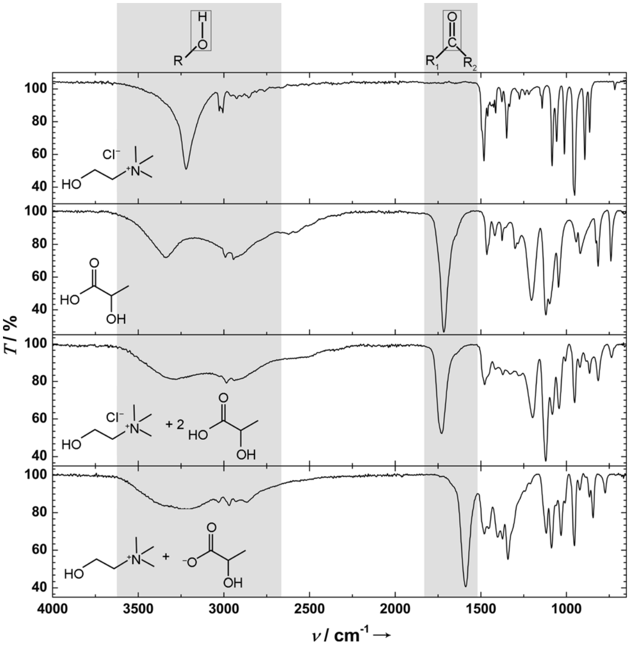


Figure 9. FT-IR spectra of pure choline chloride, lactic acid, an LTTM of lactic acid and choline chloride (2:1 molar ratio), and the IL choline lactate.[28]

The fact that, upon mixing, the starting materials remain in their molecular state in the liquid phase allows an easy recovery of the DES after being used as solvents. The addition of any agent that is able to disrupt the intermolecular interactions leads to the recrystallization of both or one of the initial compounds (see Figure 10).[26]

An interesting insight into the molecular motion and ion diffusion in DESs can be found in a recent publication[50] which describes that the diffusion mechanism was not consistent with the conventional Stokes–Einstein equation. Instead, the assumption of IL-type behavior with discrete ions was supported, despite the high number of molecular components in the liquid. However, the free volume in DESs is larger compared to that in ILs because of a lower agglomeration of void spaces.

Another interesting advantage of DESs over ILs is that most of the former are enzyme-tolerant media. The possibility

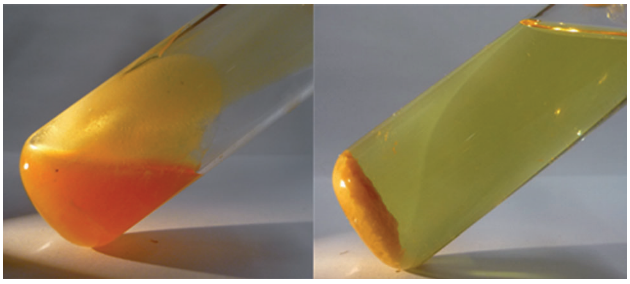


Figure 10. Precipitation of malic acid/glycine (1:1) upon addition of ethanol; 2 mL EtOH/1.5 g mixture (left); and 9 mL EtOH/1.5 g mixture (right).

to change the pH value by changing the composition or the temperature makes it easier to create an enzyme-tolerant environment. Additionally, the concentration of salt can be adjusted such that it does not not affect enzyme activity. Some LTTMs can even be formed by mixing two constituents that are not salts at all.

Lindberg et al.[51] reported DESs as promising alternatives to ILs as cosolvents for biocatalysis. As cosolvent, DESs can provide a possibility to control the regioselectivity in catalysis and hence the product purity, although they can be regarded as simple solutions of their counterparts. Gorke et al.[52] proved that the initial specific activity for transesterification catalyzed by immobilized CALB was comparable or higher in DESs than in typical ILs or conventional solvents such as toluene (Figure 11). They also observed that the initial specific activity for aminolysis in DESs was five times higher than in ILs. Finally, DESs were found suitable as cosolvents for reactions in aqueous solutions, in which they accelerate for example hydrolase-catalyzed reactions up to 20 times.

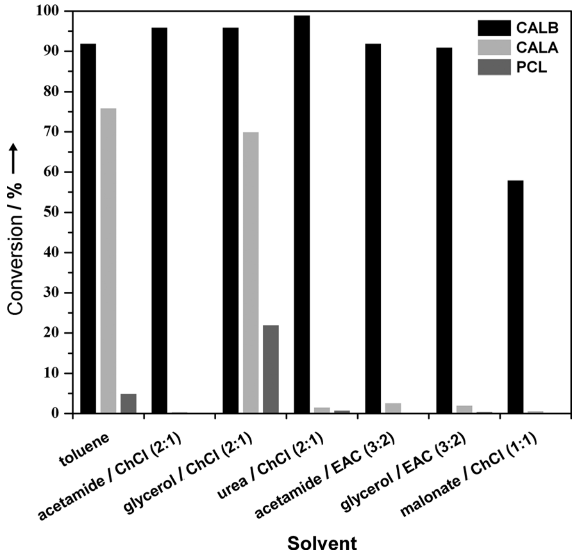


Figure 11. Conversions of the lipase-catalyzed (CALB, CALA, and PCL) transesterification of ethyl valerate with 1-butanol in toluene and DESs.[52] ChCl: choline chloride, EAC: ethyl acetate.

5. Application of LTTMs and DESs as Solvents in Process Technologies

A recent review[39] summarizes the main fields in which DESs have been applied. The first DESs reported by Abbott and co-workers were applied in the field of metal electrodeposition. As electrochemistry was the first field for DES applications, it is understandable that most of the reports are found in this field. Figure 12 shows the distribution of all publications about DESs in six main fields of applications, taking the list of publications from ISI Web of Science (September 2012) as reference.

A suitable solvent for metal electrodeposition or electrochemical reactions needs to fit the required redox-potential window. The use of ILs was explored in this field to avoid the limitations of using aqueous solutions as solvents.[53–55] DESs have the advantage of being water-tolerant, biodegradable, and cheap. They were successfully applied to metal and alloy electrodeposition,[56] separations, electropolishing,[57] and preparation of electrolytes.[58]

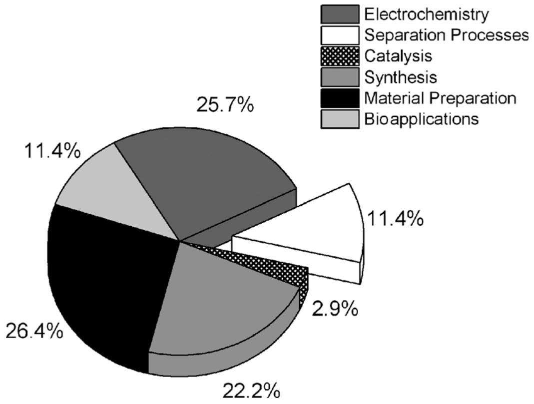


Figure 12. Relative distribution of publications on DESs by application field.

The field of material preparation using DESs is also well studied. DESs gained increasing interest as solvents and/or dispersion media for the preparation of nanoparticles. The choice of composition and water content in the DESs allows control of the size, shape, and surface structure of dispersed nanoparticles.[59,60] New open-framework structures, such as metal phosphates,[39] metal–organic frameworks,[61] and new organic–inorganic structures with special emphasis on polyoxometalate-based hybrid materials,[62] were successfully prepared in DESs.

In a comparable extension to the two fields of application described above, extensive research has been carried out on synthesis using DESs as solvents or even catalysts in reactions.[39,63–66]

These three application fields (electrochemistry, material preparation, and synthesis) account for almost 3/4 of the total number of publications. The remaining application fields are distributed between catalysis (2.9%), bio-applications (11.4%), which include biocatalysis, enzymatic reactions, biomaterials or other biotransformations, and separation processes (11.4%).

However, it is surprising that DESs are not fully explored for exploitation as much as it would be expected because of their versatile nature. The number of publications on DESs is much lower than the number of reports on ILs, but increases exponentially, as was observed for ILs during the past decade. Therefore, it is reasonable to expect increasing research activity and exploitation of DESs and LTTMs in the field of separation technology. Figure 13 shows the relative distribution of publications reporting separation processes in DESs. These reports mainly involve extractions with LTTMs for applications like the deconstruction of biomass,[28] biofuel processing,[67,68] solid-liquid separations,[69] and different processes involving two liquid phases.[70] However the number of reports on gas-separation technology and vapor–liquid equi-

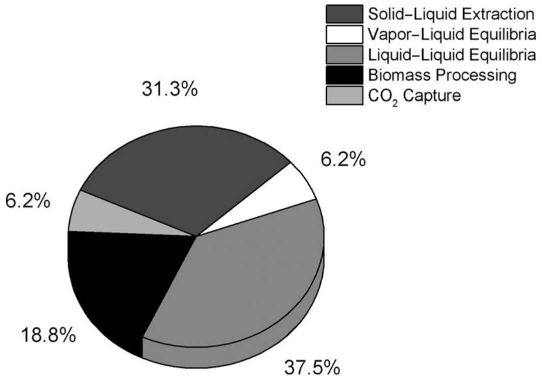


Figure 13. Relative distribution of publications reporting the use of DESs in separation processes.

librium processes are rather scarce. Only two publications were found.[71,72]

It should be mentioned that two patents were found on applications of DESs. One patent claims the use of multiple eutectic mixtures for cosmetic formulations (as referred to in Section 2),[30] and the second patent involves general applications of DESs and dates from 2011.[73]

If we make a comparison between the evolution of the possible application fields of ILs and LTTMs, we can already predict different fields in which applications for LTTMs will be explored in the following years. For example, the introduction of LTTMs in the field of biomass processing is promising, barely explored, and timely.[28] In the field of biocatalysis, DESs showed promising results as enzyme-tolerant media and biosolvents for metabolites in plants, among others. However, there are many opportunities for further research on other bioapplications. The report from Bica et al.[40] points to promising applications in the preparation of new pharmaceutical formulations and the liquefaction of drugs. In the field of separation technology, more research is expected on the optimization of DESs as solvents for CO_2 capture. Furthermore, other separation processes can be studied. Because most of the LTTMs contain a salt as one of the main constituents, it is expected that LTTMs will be used for other applications in which ILs succeeded as solvents over the past years. One of the completely unexplored fields is the use of DESs as entrainers in liquid–liquid extractions or extractive distillations.

6. New findings

Until now, all the scientific references found on the phase behavior of DESs showed a steep decrease of the freezing point of the resultant mixtures, which is dependent on the molar ratio of the constituents. However, in our group, new mixtures were formed by combination of natural HBD and HBA counterparts.[28] For the determination of the eutectic temperature and composition, differential scanning calorimetry (DSC) analysis was carried out. Table 1 shows the glass-transition temperatures of the analyzed mixtures. Different from what was observed in all other publications, no melting points were found for the formed liquids. Instead, all of them were showing a much lower glass-transition temperature than expected.

Table 1: Glass-transition temperatures of the LTTMs measured by DSC analysis from room temperature to 183 K (−90 °C).

Name	Hydrogen-Bond Donor	Ratio	Hydrogen-Bond Acceptor	T_g
LA 9:1	lactic acid	9:1	alanine	−59.31
LB 2:1	lactic acid	2:1	betaine	−46.86
LC 1.3:1	lactic acid	1.3:1	choline chloride	−76.75
LC 2:1	lactic acid	2:1	choline chloride	−77.73
LC 5:1	lactic acid	5:1	choline chloride	−69.23
LC 10:1	lactic acid	10:1	choline chloride	−66.3
LG 9:1	lactic acid	9:1	glycine	−54.51
LH 9:1	lactic acid	9:1	histidine	−39.22
LP 2:1	lactic acid	2:1	proline	−36.69
MA 1:1	malic acid	1:1	alanine	−42.64
MB 1:1	malic acid	1:1	betaine	−20.01
MC 1:1	malic acid	1:1	choline chloride	−56.48
MG 1:1	malic acid	1:1	glycine	−34.08
MP 1:1	malic acid	1:1	proline	−13.64
MP 1:2	malic acid	1:2	proline	−15.51
MP 1:3	malic acid	1:3	proline	−44.38
MH 2:1	malic acid	2:1	histidine	–[a]
MN 9:1	malic acid	9:1	nicotinic acid	–[a]
OB 1:1	oxalic acid dihyd.[b]	1:1	betaine	−17.19
OP 1:1	oxalic acid dihyd.[b]	1:1	proline	−42.91
OC 1:1	oxalic acid dihyd.[b]	1:1	choline chloride	−40.17
OG 3:1	oxalic acid dihyd.[b]	3:1	glycine	–[a]
ON 9:1	oxalic acid dihyd.[b]	9:1	nicotinic acid	–[a]
OH 9:1	oxalic acid dihyd.[b]	9:1	histidine	–[a]
OCA 1:1	oxalic acid anhyd.[b]	1:1	choline chloride	−46.06
OPA 1:1	oxalic acid anhyd.[b]	1:1	proline	−14.45

[a] No transition was found. [b] dihyd. = dihydrate, anhyd. = anhydrous.

Because most of the mixtures showed glass transitions instead of melting points, we named them "low-transition-temperature mixtures" (LTTMs), and not DESs. Some examples of DSC curves of these mixtures are shown in Figure 14.[28] As explained in the previous section, the same findings were reported about the "liquid cocrystals" formed by mixing lidocaine with different fatty acids.[40]

Because of the ambivalence with regard to the type of phase transition involved, a mixture that was known to have a eutectic point[34] (anhydrous oxalic acid/choline chloride)

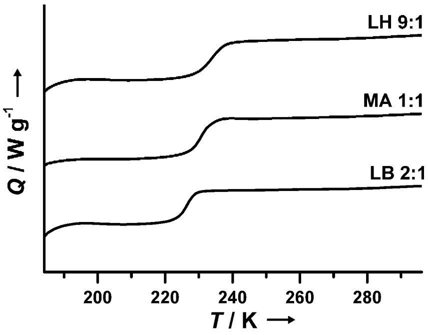


Figure 14. DSC curves for the mixtures of lactic acid/histidine (LH 9:1), malic acid/alanine (MA 1:1), and lactic acid/betaine (LB 2:1).

was prepared. However, in accordance with the other prepared LTTMs, no melting temperature was observed, but a glass transition was found instead. Besides that, no crystallization was observed at room temperature, while crystal formation was previously reported to occur just above 298 K.[34] This difference could be explained by the synthetic method.

The preparation method is of great importance in the formation of molecular complexes in the liquid phase. The one reported method consists of melting one of the starting materials (the one that has the lower melting point) and adding the second component in its solid state. The mixture is then stirred until a clear liquid is formed. When both of the starting materials have very high melting points or relatively high thermal instability, this method cannot be applied.

We developed a different preparation method: both of the starting materials were mixed in the solid state at room temperature in order to promote contact between the solid crystals. The vessel containing the mixtures was sealed and the temperature was increased very slowly until a certain limit was reached. The resulting liquid phase was stirred until a clear liquid was formed. Several experiments were carried out to find the lowest possible temperature of formation. The lower the preparation temperature, the longer it takes until no solid particles remain in the mixtures. Following the described procedure, we were able to prepare LTTMs that show much higher thermal stability and liquid range. No freezing points were found (Figure 14). This behavior is more typical for a liquid crystal or an IL than for a eutectic mixture.

Previously, Choi et al.[25] observed intermolecular interactions in malic acid/sucrose mixtures similar to the ones found in liquid crystals by using ^{1}H–^{1}H nuclear Overhauser enhancement spectroscopy. Morrison et al.[74] studied the thermal behavior of the eutectic mixtures formed by choline chloride and urea. Their DSC analysis of the 2:1 mixture showed both glass formation and melting/crystallization. On the other hand, the malonic acid/choline chloride mixture did not show any thermal events upon cooling. The researchers concluded that nucleation and crystal growth might be prevented by the high viscosity of the DES.[74]

for industrial applications. In this line, the study of mixtures with other additives or cosolvents would be of great help. For example, the effect of water addition on different properties was found to be not only predictable, but also of use to design new tailor-made LTTMs.

However, LTTMs are not only advantageous compared to ILs or other conventional solvents. Some of them also have important drawbacks related to their thermal stability and their non-negligible vapor pressure. The thermal stability of LTTMs is not always guaranteed by the thermal stability of the starting materials, because of the presence of hydrogen bonding and electrostatic interactions. The liquids formed by strong intermolecular interactions showed high stability upon heating without appreciable weight loss.[74] For weaker hydrogen-bonding interactions, the strength of the bonds decreased with increasing temperature. This is common behavior for molecular hydrogen-bonding substances in, for example, water. Not all of the LTTMs showed higher thermal stability compared to their starting materials (Figure 15). Another limitation related to their hydrogen-bonding nature is the impossibility to form a water-insoluble DES, which could be used to form biphasic mixtures with water.

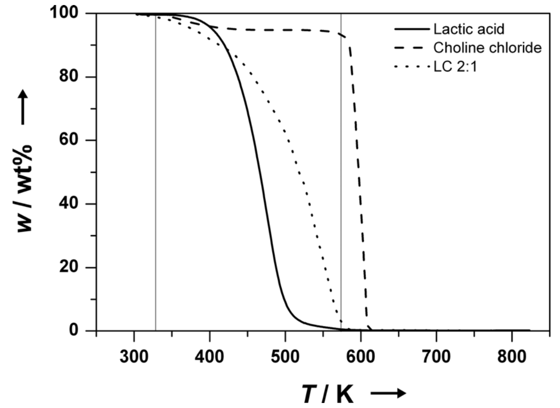


Figure 15. TGA curves of LC 2:1 and its constituents; the vertical lines mark the transition temperatures of the constituents. Experimental data measured in our group (unpublished results).

7. Challenges and Limitations of LTTMs and DESs

The lack of experimental data about the preparation and properties of LTTMs makes it difficult to gain a clear insight into the building principles, feasible mechanisms of formation, and intermolecular interactions. A deeper fundamental study would be necessary to reach unambiguous conclusions.

Most of the LTTMs and DESs exhibit physical and thermodynamical behavior similar to that found for ILs. However, both the physical properties and solubilities of different substances in the newly explored solvents are largely unknown, and predictive methods are unavailable. The prediction of some properties, such as viscosity and thermal behavior, would be of high interest for the selection of components that can form an LTTM for a specific application. For example, most of the LTTMs formed using amino acid components exhibit very high viscosity, which is not desired

LTTMs and DESs are generally claimed to be biodegradable and environmentally friendly, but this classification depends exclusively on the selected constituents. In some cases, LTTMs and DESs can be formed using nonbiofriendly substances (as most ILs), for example, with imidazole or methyltriphenylphosphonium bromide.[39] A detailed life-cycle assessment of new solvents for a certain application would be necessary in order to claim their suitability from a "green chemistry" point of view.

8. Conclusions

DESs among LTTMs are a family of new "designer solvents" that were found to be greener and cleaner alternatives to conventional molecular solvents or ILs. LTTMs show the advantage of having promising solvent qualities. Unlike most ILs, they can be prepared from cheap and natural starting materials, contributing to their sustainable characteristics. They can be prepared by mixing different families of substances that show strong intermolecular hydrogen-bonding interactions. Their properties and phase behavior can be tailored by choosing both the nature and ratio of the counterparts.

Promising results were found for different fields of applications. However, the field of separation technology is still far from being fully explored. Deeper studies on the interactions and building principles are needed in order to gain insight into the properties of these solvents and to find new applications.

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