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

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Apr. 08, 2013
Introduction
Introduction

The disadvantage of the conventional organic solvents

- known to be toxic
- dangerous for large-scale applications
- expensive to dispose as waste

In order to solve the problem

- water, glycerol, poly(ethylene glycol), perfluorinated solvents,
- ethyl lactate, supercritical fluids, or ionic liquids (ILs), and so on.

The disadvantage of ionic liquids

1. The hazardous toxicity and the very poor biodegradability of most ionic liquids
2. Ionic liquids with high purity are required
3. The high price of common ionic liquids
Introduction

To overcome the high price and toxicity of ionic liquids

In 2003, Abbott presented a new type of green solvents
the low-transition-temperature mixtures (LTTMs)
LTTMs 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.

The advantage of DESs
- cheap and easy to prepare from natural and readily available starting materials, biodegradable, and renewable
Definition of DESs

DESs is a fluid generally composed of two or three cheap and safe components that are capable of self-association, often through hydrogen bond interactions, to form a eutectic mixture with a melting point lower than that of each individual component.
Syntheses

DES is obtained by mixing a quaternary ammonium salt with metal salts or a hydrogen bond donor (HBD) that has the ability to form a complex with the halide anion of the quaternary ammonium salt.

Typical structures of the halide salts and hydrogen bond donors used for DES syntheses.

Scheme 1  Preparation of deep eutectic solvent.
In 2007, Abbott and co-workers defined DESs using the general formula $R_1R_2R_3R_4N^+X^-Y^-$. 

Type I DES $Y = MCl_x$, $M = Zn, Sn, Fe, Al, Ga$

Type II DES $Y = MCl_xyH_2O$, $M = Cr, Co, Cu, Ni, Fe$

Type III DES $Y = R_5Z$ with $Z = -CONH_2, -COOH, -OH$

Type IV DES = metal chlorides (e.g. $ZnCl_2$) mixed with different HBDs such as urea, ethylene glycol, acetamide or hexanediol

Synthesis of DESs is 100% atom economic, easy to handle and no purification is required, thus making their large-scale use feasible.
**Physicochemical properties**

**DESs** are chemically tailorable solvents since they can be designed by properly combining various *quaternary ammonium salts* (e.g. ChCl) with *different hydrogen bond donors* (HBD). Hence, task-specific DESs with different physicochemical properties can be prepared.

Freezing point ($T_f$)  Density  Viscosity  Polarity  Conductivity
Physicochemical properties

Freezing point ($T_f$)

DESs are formed by mixing two solids capable of generating a new liquid phase by self-association via hydrogen bonds. This new phase is generally characterized by a lower freezing point than that of individual constituents.

$$\text{melting point}$$  $$\text{melting point}$$  $$\text{freezing point}$$

<table>
<thead>
<tr>
<th></th>
<th>DESs</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 $^\circ$C</td>
<td></td>
</tr>
<tr>
<td>ratio</td>
<td>1</td>
<td>2</td>
<td>12 $^\circ$C</td>
<td></td>
</tr>
<tr>
<td>melting point</td>
<td>302 $^\circ$C</td>
<td>133 $^\circ$C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all reported DESs, their freezing points are below 150 $^\circ$C. Generally, DESs with a freezing point lower than 50 $^\circ$C are more attractive since they can be used as inexpensive and safe solvents in many fields.
Abbott and co-workers proposed that the freezing point of HBD-salt eutectic mixtures should be dependent on

(1) the lattice energies of DESs

(2) the way how the couple anion-HBD interacts

(3) the entropy changes arising from the formation of a liquid phase

The density is one of the most important physical properties for a solvent. Densities of DESs are determined by means of a specific gravity meter.

<table>
<thead>
<tr>
<th>Salts</th>
<th>HBD</th>
<th>Salt : HBD (mol : mol)</th>
<th>Density ($\rho$, g cm$^{-3}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtNH$_3$Cl</td>
<td>CF$_3$CONH$_2$</td>
<td>1 : 1.5</td>
<td>1.273</td>
</tr>
<tr>
<td>EtNH$_3$Cl</td>
<td>Acetamide</td>
<td>1 : 1.5</td>
<td>1.041</td>
</tr>
<tr>
<td>EtNH$_3$Cl</td>
<td>Urea</td>
<td>1 : 1.5</td>
<td>1.140</td>
</tr>
<tr>
<td>ChCl</td>
<td>CF$_3$CONH$_2$</td>
<td>1 : 2</td>
<td>1.342</td>
</tr>
<tr>
<td>AcChCl</td>
<td>Urea</td>
<td>1 : 2</td>
<td>1.206</td>
</tr>
<tr>
<td>ChCl</td>
<td>Urea</td>
<td>1 : 2</td>
<td>1.25</td>
</tr>
<tr>
<td>ZnCl$_2$</td>
<td>Urea</td>
<td>1 : 3.5</td>
<td>1.63</td>
</tr>
<tr>
<td>ZnCl$_2$</td>
<td>Acetamide</td>
<td>1 : 4</td>
<td>1.36</td>
</tr>
<tr>
<td>ZnCl$_2$</td>
<td>EG</td>
<td>1 : 4</td>
<td>1.45</td>
</tr>
<tr>
<td>ZnCl$_2$</td>
<td>Hexanediol</td>
<td>1 : 3</td>
<td>1.38</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glycerol</td>
<td>1 : 2</td>
<td>1.18</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glycerol</td>
<td>1 : 3</td>
<td>1.20</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glycerol</td>
<td>1 : 3</td>
<td>1.20</td>
</tr>
<tr>
<td>ChCl</td>
<td>EG$^b$</td>
<td>1 : 2</td>
<td>1.12</td>
</tr>
<tr>
<td>ChCl</td>
<td>EG</td>
<td>1 : 3</td>
<td>1.12</td>
</tr>
<tr>
<td>ChCl</td>
<td>Malonic acid</td>
<td>1 : 2</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Most of DESs exhibit higher densities than water.
Physicochemical properties

Density

The density of a glycerol/ChCl DES as a function of the molar composition.

The organic salt/HBD molar ratio has an obvious effect on the densities of DES.

Except for ChCl-ethylene glycol(EG) eutectic mixture, most of the DESs exhibit relatively high viscosities (>100 cP) at r.t. The high viscosity of DESs is often attributed to the presence of an extensive hydrogen bond network between each component, which results in a lower mobility of free species within the DES.

The high viscosity of DES should be dependent on

1. the large ion size
2. small void volume of most DESs
3. electrostatic
4. van der Waals interactions
### Physicochemical properties

The viscosity data of common DESs at different temperatures.

<table>
<thead>
<tr>
<th>Organic Salts</th>
<th>HBD</th>
<th>Salt : HBD molar ratio</th>
<th>Viscosities (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChCl</td>
<td>Urea</td>
<td>1 : 2</td>
<td>750 (25 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Urea</td>
<td>1 : 2</td>
<td>169 (40 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>EG</td>
<td>1 : 2</td>
<td>36 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>EG</td>
<td>1 : 2</td>
<td>37 (25 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>EG</td>
<td>1 : 3</td>
<td>19 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>EG</td>
<td>1 : 4</td>
<td>19 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glucose</td>
<td>1 : 1</td>
<td>34 400 (50 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glycerol</td>
<td>1 : 2</td>
<td>376 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glycerol</td>
<td>1 : 2</td>
<td>259 (25 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glycerol</td>
<td>1 : 3</td>
<td>450 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Glycerol</td>
<td>1 : 4</td>
<td>503 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>1,4-Butanediol</td>
<td>1 : 3</td>
<td>140 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>1,4-Butanediol</td>
<td>1 : 4</td>
<td>88 (20 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>CF$_3$CONH$_2$</td>
<td>1 : 2</td>
<td>77 (40 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Imidazole</td>
<td>3 : 7</td>
<td>15 (70 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>ZnCl$_2$</td>
<td>1 : 2</td>
<td>85 000 (25 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Xylitol</td>
<td>1 : 1</td>
<td>5230 (30 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Sorbitol</td>
<td>1 : 1</td>
<td>12 730 (30 °C)</td>
</tr>
<tr>
<td>ChCl</td>
<td>Malonic acid</td>
<td>1 : 2</td>
<td>1124 (25 °C)</td>
</tr>
</tbody>
</table>
An increase of the ChCl/glycerol molar ratio results in a decrease of the DES viscosity.
Polarity of a solvent can be evaluated by its polarity scale, $E_T(30)$, which is the electronic transition energy of a probe dye (e.g. Reichardt’s Dye 30) in a solvent.

$$E_{T}(30) \text{(kcal mol}^{-1} \text{)} = h \nu_{\text{max}} N_A = (2.8591 \times 10^{-3}) \nu_{\text{max}} \text{(cm}^{-1}) = 28591/\lambda_{\text{max}}$$

A roughly linear increase of $E_T(30)$ with the ChCl concentration was observed.
Physicochemical properties

Ionic conductivity

Conductivities of DESs generally increase significantly as the temperature increases due to a decrease of the DES viscosity.
As compared to another solvent, DESs have notable advantages stemming from:

1. their convenient synthesis (100% atom economy)
2. their very low price since most of DESs can be prepared from readily accessible chemicals
3. their low toxicity, especially DESs derived from ChCl and renewable chemicals

Although components of DESs are potentially reactive chemicals, their auto-association by a hydrogen bond drastically limits their reactivity, allowing their use in many fields of research.
Combination of CO₂ with green DES systems has a great potential for a variety of chemical processes (separation and purification of gas, chemical fixation of CO₂, catalysis, etc.).

In 2008, Han and co-workers determined the solubility of CO₂ in a ChCl/urea DES at different temperatures, pressures and with different ChCl/urea molar ratio.

The solubility of CO₂ ($x_1$) in ChCl/urea DES depends on three factors:
1. $x_1$ values increased with increase in the CO₂ pressure (solubility of CO₂ is more sensitive to the pressure in the low-pressure range)
2. $x_1$ values decreased with increase in the temperature whatever the pressure
3. the ChCl/urea molar ratio has a significant effect on $x_1$ values
   (e.g. at the same temperature and pressure, the ChCl-urea (1 : 2) eutectic mixture exhibits higher $x_1$ values than DES with a ChCl/urea molar ratio of 1 : 1.5 and 1 : 2.5)
Dissolution in DESs

Dissolution of metal oxides

DESs are capable of **donating** or **accepting** electrons or protons to form **hydrogen bonds** which confers them excellent dissolution properties. DESs are capable of dissolving various **metal oxides**, thereby opening a “green” strategy for the separation and recycling of metals, a key point in electrochemistry technology.

<table>
<thead>
<tr>
<th>DESs</th>
<th>CuO</th>
<th>Fe$_3$O$_4$</th>
<th>ZnO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChCl/malonic acid</td>
<td>0.246</td>
<td>0.071</td>
<td>0.554</td>
</tr>
<tr>
<td>ChCl/oxalic acid</td>
<td>0.071</td>
<td>0.341</td>
<td>0.491</td>
</tr>
<tr>
<td>ChCl/phenylpropionic acid</td>
<td>0.473</td>
<td>0.014</td>
<td>&gt;0.491</td>
</tr>
</tbody>
</table>

Solubility of ZnO, CuO, and Fe$_3$O$_4$ in three DESs at 50 °C

Dissolution in DESs

Dissolution of metal oxides

Solubility of metal oxides in a ChCl/urea (1 : 2) at 60 °C

<table>
<thead>
<tr>
<th>Metal oxides</th>
<th>mp/°C</th>
<th>Solubility*/ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al₂O₃</td>
<td>2045</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CaO</td>
<td>2580</td>
<td>6</td>
</tr>
<tr>
<td>CuO</td>
<td>1326</td>
<td>470</td>
</tr>
<tr>
<td>Cu₂O</td>
<td>1235</td>
<td>8725</td>
</tr>
<tr>
<td>Fe₂O₃</td>
<td>1565</td>
<td>49</td>
</tr>
<tr>
<td>Fe₃O₄</td>
<td>1538</td>
<td>40</td>
</tr>
<tr>
<td>MnO₂</td>
<td>535</td>
<td>493</td>
</tr>
<tr>
<td>NiO</td>
<td>1990</td>
<td>325</td>
</tr>
<tr>
<td>PbO₂</td>
<td>888</td>
<td>9157</td>
</tr>
<tr>
<td>ZnO</td>
<td>1975</td>
<td>8466</td>
</tr>
</tbody>
</table>

*The metal solubility was determined using ICP-AES.

Dissolution of metal oxides in ChCl/urea DES is mainly governed by the complexation abilities of urea and the chloride anion.
Many DESs have excellent dissolution properties for CO$_2$, inorganic salts, and organic molecules.

Many DESs can selectively dissolve different metal oxides, which thus provide great potential for the selective recovery of pure metals, especially in electrochemistry.
Catalysis in DESs

Base-catalyzed reactions

Electrophilic substitution of 1-aminoanthra-9,10-quinone derivatives in ChCl/urea (1 : 2).

\[
\text{Aminoanthraquinone} \xrightarrow{\text{ChCl/urea (1:2), 80°C}} \text{Amino mono/dibromo anthraquinone}
\]

\[
R_1 = -H \text{ or } -\text{Cl}
\]
\[
R_2 = -H \text{ or } -\text{Me}
\]

\[
\text{yield} = 84-95\%
\]

this rate enhancement might be attributed to the basic nature of the DES and/or to the ability of urea to stabilize transition states

Catalysis in DESs

Base-catalyzed reactions

Base-catalyzed Knovenagel in the ChCl-urea (1 : 2) system.

This DES was successfully recycled five times thanks to the easy isolation of the products of the reaction from the DES phase.

Catalysis in DESs

Acid-catalyzed reactions

Acid-catalyzed dehydration of inulin and fructose in ChCl-derived DES.

Catalysis in DESs

Acid-catalyzed reactions

Selectively prepare $\alpha$-mono or $\alpha,\alpha$-dichloro ketones and $\beta$-ketoesters

Using a DES (choline chloride:$p$-TsOH = 1:1) as the solvent and stirring for 45 min at r.t., $\alpha,\alpha$-dichlorinated products were selectively obtained in 86-95% yield.

Catalysis in DESs

Acid-catalyzed reactions

Synthesis of bis(indolyl)methane in acid derived ChCl DESs.

Catalysis in DESs

Transition-metal-catalyzed reactions

Palladium-catalyzed Suzuki coupling in various carbohydrate-urea-inorganic salts eutectic mixtures.

\[
\text{Pd(OAc)}_2 \text{(10 mol%), 90°C, 1.2 eq Na}_2\text{CO}_3, 6\text{h} \]

\[
\begin{align*}
\text{R} & = -\text{H}, 4\text{-methyl, 2,6-dimethyl} \\
\end{align*}
\]

\[
\begin{align*}
\text{fructose/urea/NaCl (7:2:1)} \\
\text{maltose/DMU/NH}_4\text{Cl (5:4:1)} \\
\text{mannose/DMU (3:7)} \\
\text{lactose/DMU/NH}_4\text{Cl (6:3:1)} \\
\text{mannitol/DMU/NH}_4\text{Cl (5:4:1)} \\
\text{sorbitol/DMU/NH}_4\text{Cl (7:2:1)} \\
\text{glucose/urea/NH}_4\text{Cl (6:3:1)}
\end{align*}
\]

yield = 78-98%
Catalysis in DESs

Transition-metal-catalyzed reactions

Palladium-catalyzed Heck coupling in D-mannose/N,N-dimethylurea melts.

\[
\begin{align*}
R = -H, -OMe, -NO_2, -Br \\
Pd = Pd(OAc)_2, PdCl_2(PPh_3)_2 \\
L-Carnitine/urea (2:3), [Pd] 1\text{mol\%}, 80^\circ \text{C}, 18h \\
R = -Br & \quad Pd(OAc)_2, \text{yield} = 75\% \\
& \quad PdCl_2(PPh_3)_2, \text{yield} = 62\%
\end{align*}
\]

Catalysis in DESs

Transition-metal-catalyzed reactions

Sonogashira coupling in D-mannose/ N,N-dimethylurea melts.

Catalysis in DESs

Transition-metal-catalyzed reactions

Palladium-catalyzed Stille coupling of aryl bromide and iodide with alkyl and aryl stannate in polyol/ N,N-dimethylurea /NH₄Cl melts.

Catalysis in DESs

Transition-metal-catalyzed reactions

Cu-catalyzed azide-alkyne 1,3-dipolar cycloaddition in D-sorbitol/urea/NH₄Cl or L-carnitine/urea melts.

Catalytic hydrogenation of methyl α-cinnamate in citric acid/ N,N-dimethylurea (2:3).

activity of enzymes in selected DES was similar to that observed in toluene demonstrating the potential of DESs for biotransformations
Biocatalysis in DESs

Table 12 Activity and selectivity of Novozym® 435 in the transesterification of ethylsorbate with 1-propanol

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Activity/µmol min⁻¹ g⁻¹</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-Butanol</td>
<td>0.57</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>1-Propanol</td>
<td>0.10</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.71</td>
<td>38</td>
</tr>
<tr>
<td>ChCl/urea (1 : 2)</td>
<td>1.00</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>ChCl/glycerol (1 : 2)</td>
<td>1.12</td>
<td>45</td>
</tr>
<tr>
<td>ChOAc/glycerol (1 : 2)</td>
<td>0.21</td>
<td>40</td>
</tr>
<tr>
<td>ChOAc/EG (1 : 2)</td>
<td>0.07</td>
<td>12</td>
</tr>
<tr>
<td>ChOAc/glycerol (1 : 2)</td>
<td>1.02</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^{a}\) EG = ethylene glycol. \(^{b}\) EG is reactive explaining the lower selectivity.

Biocatalysis in DESs

Table 13 Activities of subtilisin and α-chymotrypsin in glycerol-derived DESs

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Protease</th>
<th>Water content (v/v)</th>
<th>Activity/μmol min⁻¹ g⁻¹</th>
<th>Scl. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Butanol</td>
<td>S/Chit</td>
<td>2</td>
<td>0.50</td>
<td>29</td>
</tr>
<tr>
<td>CHOA/glycerol (1:1.5)</td>
<td>S/Chit</td>
<td>2</td>
<td>0.42</td>
<td>99</td>
</tr>
<tr>
<td>CHOA/glycerol (1:1.5)</td>
<td>S/Chit</td>
<td>3</td>
<td>0.40</td>
<td>99</td>
</tr>
<tr>
<td>CHOA/glycerol (1:1.5)</td>
<td>S/Chit</td>
<td>4</td>
<td>0.90</td>
<td>99</td>
</tr>
<tr>
<td>CHCl/glycerol (1:2)</td>
<td>Free α-C</td>
<td>2</td>
<td>0.028</td>
<td>99</td>
</tr>
<tr>
<td>CHCl/glycerol (1:2)</td>
<td>α-C/Chit</td>
<td>2</td>
<td>0.031</td>
<td>99</td>
</tr>
<tr>
<td>CHCl/glycerol (1:2)</td>
<td>α-C/Chit</td>
<td>3</td>
<td>0.75</td>
<td>99</td>
</tr>
<tr>
<td>CHCl/glycerol (1:2)</td>
<td>S/Chit</td>
<td>3</td>
<td>2.90</td>
<td>98</td>
</tr>
</tbody>
</table>

*50 °C, S = subtilisin, α-C = α-chymotrypsin, Chit = chitosan.

Indicating that glycerol-derived DESs were very attractive for biocatalytic reactions involving more sensitive enzyme than lipase.

The remarkable stability of enzymes in DESs has been recently highlighted in a scientific correspondence. Some authors have hypothesized that the formation of natural DESs from chemicals that are present at high concentration in living cells may contribute to explain (1) mechanisms and phenomena that are nowadays difficult to understand (2) the resistance of living organisms under extreme conditions.

Organic synthesis in DESs

Example of Biginelli reaction performed in acid L-(+)-tartaric acid/DMU (3 : 7) DES.

Urea was used in this example not only as a reactant but also as a component of the DES.

Ex: in a citric acid/DMU (2 : 3) DES, p-4-nitrobenzaldehyde, ethylacetoacetate and DMU were selectively assembled at 65 °C to the desired DHPM which was obtained with 90% yield.

Organic synthesis in DESs

Table 14: Three component reactions of 2-amino-benzophenone, 4-nitrobenzaldehyde and ammonium acetate in various DESs

This work exhibited a broad substrate scope and products of the reaction were conveniently isolated from the DES either by crystallization or by extraction with ethyl acetate, allowing the DES to be recycled.
Organic synthesis in DESs

Reduction of aldehydes and epoxides by NaBH₄ in ChCl/urea.

In the field of catalysis and organic synthesis, it is clear that DESs will definitely contribute to the design of eco-efficient processes. The possibility to
(1) selectively and conveniently extract products of the reaction from the DESs phase
(2) adjust the pH of DESs
(3) dissolve not only organic and inorganic salts but also transition metal-derived complexes or nanoparticles
(4) recycle these media is among the most promising advantages of DESs
Outlook

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.

DESs can be regarded as a poorly toxic and biocompatible lipotropic agent, thus opening a new strategy for the vectorisation of pharmaceutical ingredients in the human body. DES’s low ecological footprint and attractive price will definitely contribute to the industrial emergence of this new medium in a close future.
Thanks for your attention!