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Basicity and Stability of the Urea Deep Eutectic Mixtures

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The stability and the basicity origin of some common urea based deep eutectic mixtures/solvents (DES) were studied. We have observed an unexpected Hantzsch dihydropyridine reaction in sorbitol/urea DES, where the source of ammonia was found not to be originated from the individual ingredients of the DES. Our results showed that decomposition of urea occur in DES at lower than expected temperatures, namely below 100°C and is enhanced in diols DES by the formation of carbonates causing their unexplained basicity. Carbohydrates and Choline chloride (ChCl) DES exhibit lower rates of decomposition, while no decomposition was observed from neat urea or MeOH and EtOH urea solutions.

Introduction

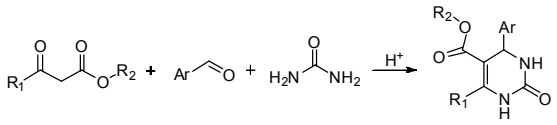
During the last decades immerged considerable scientific interest on more green and sustainable approaches in organic synthesis.[1-2] Ionic liquids (ILs) were intensively studied as promising green solvents and catalysts for diverse organic transformations.[3-5] They are considered green mainly due to their low vapour pressure, high thermal stability and recyclability but despite that there are some serious doubts about their real greenness when their all life cycle and the toxic and environmental effects during the synthesis, application and deposal are considered.[6-7] More recently, after the pioneer and systematic research of Abbott *et al.*[8-10] a new class of ionic fluids emerged namely deep eutectic mixtures/solvents (DES), which exhibit similar properties as the traditional ILs but being much more eco-friendly and cheap are of a growing interest.[11-12]

DES are typically formed by two or three components which interact each other mainly *via* hydrogen bond interactions to form an eutectic mixture, which has melting point lower than each of the individual ingredients. Most of them are liquid at temperatures below 70°C and even at RT, and can be used as safe and inexpensive solvents for diverse applications. Usually DES are obtained by mixing quaternary ammonium salts with metal salts or hydrogen bond donors (HBD).[13-15] Among all the HBD, urea is one of the most widely used because it is cheap, readily available and non-toxic. Urea based DES are already applied as solvents for various classical organic reactions[13, 16-20] and valorisation of biorenewable resources.[21-22] Many of these transformations require reaction temperatures up to 100°C and although some of them could proceed at lower temperatures the initial formation of the DES is usually performed by heating the ingredients till homogeneous mixture is formed. Herein are provided some insides on the stability of choline chloride (ChCl), polyalcohols and carbohydrates DES with urea under heating and the origin of their already observed basicity[23] and catalytic activity in base catalysed reactions.[16-17, 19-20]

Results and Discussion

In our research we were interested on the possible application of chiral DES in asymmetric synthesis and in particular asymmetric Biginelli reactions. Such an alternative would be highly attractive because DES can be easily accessed from cheap and environmental friendly natural compounds like carbohydrates or derived polyols.

The Biginelli reaction is an acid-catalysed, three-component reaction between an aldehyde, ß-ketoester and urea providing dihydropyrimidones,[24] compounds with interesting pharmacological properties associated with their heterocyclic scaffold[25] (Scheme 1).



Scheme 1

Initially we carried out classical Biginelli reaction between ethyl acetoacetate and *p*-tolyl aldehyde catalysed by *p*-toluene sulfonic acid (p-TSA) at 90°C in sorbitol/urea (47mol%/53mol%) DES. The resulting dihydropyrimidone **1**

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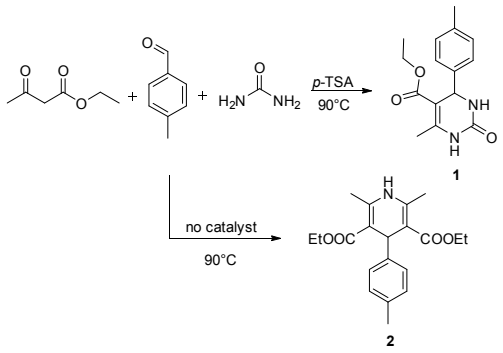
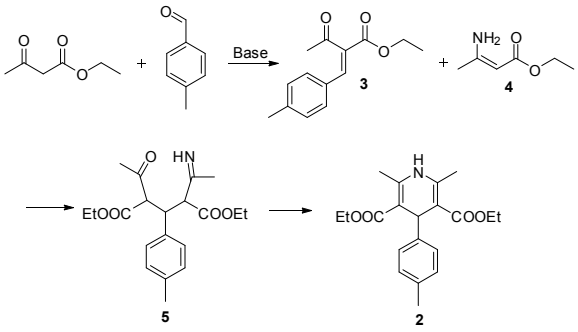
was obtained in 95% yield after 12h, with no enantiomeric excess. Surprisingly when the same reaction was repeated in absence of *p*-TSA instead of **1** we observed a new product in 41% yield, which was determined to be diethyl 2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate **2** (Scheme 2).



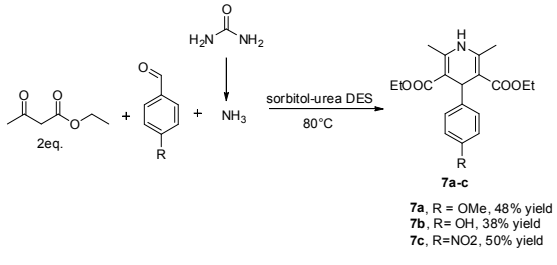
Scheme 2

Obviously the formation of **2** was a result of Hantzsch dihydropyridine synthesis[26] that proceed *via* initial Knovenagel condensation between 1 equiv. ethyl acetoacetate and p-tolyl aldehyde to form intermediate **3,** which further reacts with ester enamine **4**, produced by the condensation of a second equivalent of ethyl acetoacetate with ammonia. The formed intermediate **5** undergo cyclization to give **2** (Scheme 3).



Scheme 3

Different aryl aldehydes were screened under the same conditions and 1,4-dihydropyridine derivatives **7a-c** were obtained in moderate yields of up to 50% (Scheme 4).



Scheme 4

The unexpected formation of 1,4-dihydropyridine derivatives raises the question about the origin of ammonia in the reaction mixture. We used standard Nestler reagent test, which gives yellow colour in presence of ammonia (Figure 1). The blank tests of pure urea and sorbitol water solutions were negative (Table 1), thereby proving that ammonia is not originated as an impurity in the individual ingredients of the DES. Positive result was observed only for aqueous solution of sorbitol/urea DES (Table 1, Figure 1), which is somehow unexpected since the significant thermal urea decomposition requires higher temperatures, above 150°C.[27] However, this observation leads to the idea that partial decomposition of urea to ammonia occurs during the heating and formation of urea based DES and is responsible for their basicity.[23] Ammonia could also be the catalyst in the reported base catalysed reactions, such as Perkin[17] and Knovenagel condensations.[19]

$$NH_4+ + 2[HgI_4]^{2-} + 4OH^- \rightarrow \underset{\text{yellow color}}{HgO{\cdot}Hg(NH_3)I} + 7I^- + 3H_2O$$

Figure 1. Observed positive Nestler test (aqueous solution) for sorbitol/urea (3 h, 80°C)

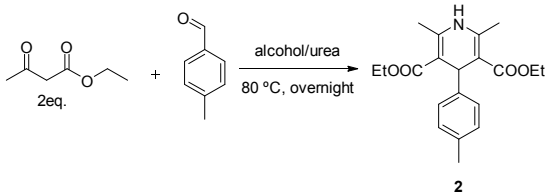
Table 1. Nestler reagent test results.

Entry	Tested mixture	Result
1	Sorbitol/Urea (47mol%/53mol%)[a]	positive
2	Urea aqueous solution[b]	negative
3	Sorbitol aqueous solution[b]	negative

[a] Prepared by heating sorbitol and urea mixture for 3h at 80°C. [b] 0.1g solution in 4 mL of distilled water.

The synthesis of **2** was later used as a clock reaction for the decomposition of urea in different alcohols. The reactions were monitored by TLC (Table 2).

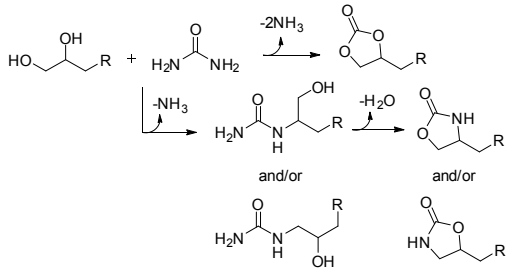
Table 2 Screening of the effect of the alcohol structure on the formation of **2**.[a]



Entry	Alcohol	Result[b]
1	Methanol	No reaction
2	Ethanol	No reaction
3	ChCl	Traces
4	Sorbitol	Product
5	Glycerol	Product

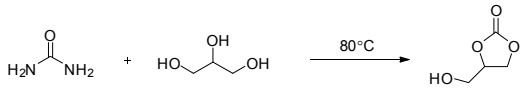
[a] *Each reaction was performed overnight at 80°C using 1:1 w/w ratio of the alcohol and urea.* [b] *Product detected by TLC*

The formation of **2** was found to be enhanced in presence of poly alcohols (2, entries 4 and 5), while no product was detected in presence of mono alcohols (Table 2, entries 1 and 2), thereby bringing to the idea that the formation of ammonia is not a result of a simple urea thermal decomposition. According to the results, the most rationalized explanation of the ammonia origin is the possible formation of cyclic carbonates and their related intermediates from the reaction of urea with poly alcohols (Scheme 5) that can proceed at moderate temperatures, even below 100°C.



Scheme 5

The formation of cyclic carbonates has been confirmed in a test reaction where a mixture of glycerol and urea (5:2 molar ratio) was heated at 80°C with steering for 3 weeks to form glycerol carbonate **6** (Scheme 6).



Scheme 6

The reaction mixture was analysed by MS (Figure 2) and ^{13}C NMR (Figure 3). The formation of **6** together with other minor side products, which were not assigned, was confirmed..

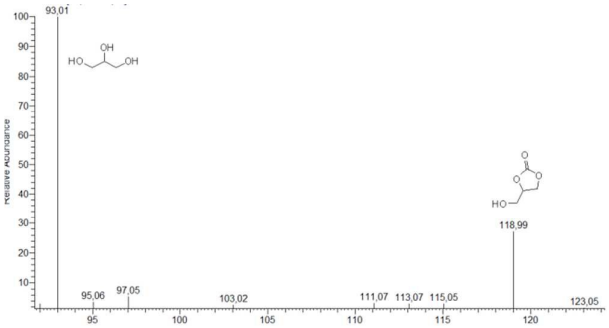


Figure 2. MS spectra of glycerol urea mixture (5:2 molar ratio, 80°C, 3 weeks)

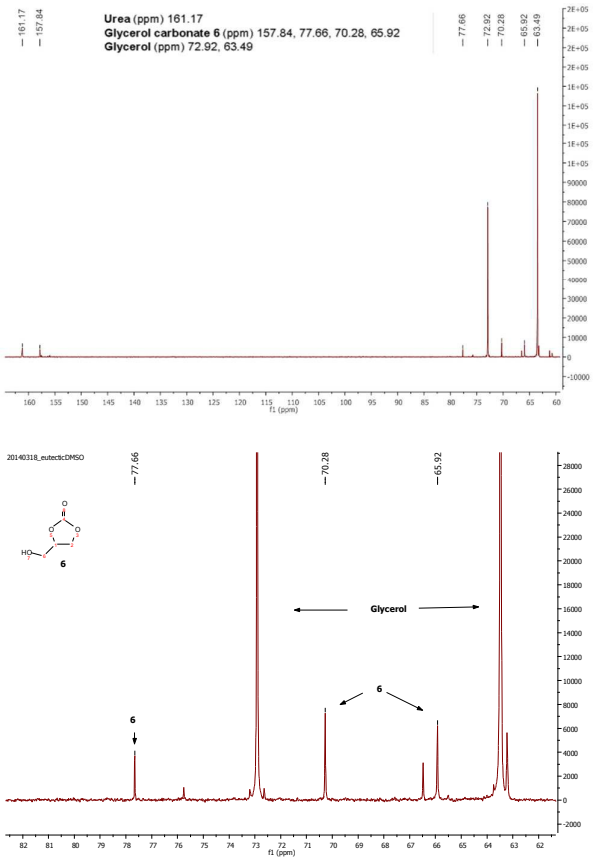
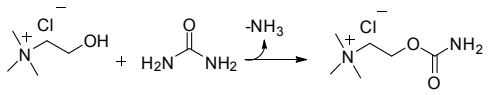


Figure 3. ^{13}C NMR of glycerol:urea mixture (5:2 molar ratio, 80°C, 3 weeks), in DMSO-d6

Our results could also explain the basicity of one of the most commonly used ChCl/urea (1:2), in which some urea decomposition occurred and traces of product **2** were observed by TLC (Table 2, entry 3). We speculate that the lower amount of formed ammonia is due to the fact that ChCl, being mono alcohol, cannot form cyclic carbonates *via* favourable intermolecular cyclization (Scheme 7).



Scheme 7

Having these results in hands, we explored the stability of some already reported DES in a systematic way. The liberated ammonia during the formation of DES was trapped in an aqueous acid solution and after titration with a base, in presence of an indicator, the amount of ammonia was determinedand could be directly related to the urea decomposition rate. The temperature of 80°C was chosen for our study because it can mimic commonly used by many researchers conditions for the formation of DES. A scale of 2.4g of urea or dimethylurea (DMU) was used for the synthesis of DES and the other ingredients were recalculated as they are

reported in the literature. In a standard experiment DES was heated at 80°C for 7h and continuously flashed with N_2, which was then bubbled trough 10mL 0.05M water solution of H_2SO_4. At the end, the solution was titrated with 0.05M solution of KOH using phenolphthalein as indicator, the results are summarized in Table 3.

Table 3. Results from the titration of the captured ammonia in 10 mL 0.05M water solution of H_2SO_4 after 7h at 80°C.

Entry	DES/molar ratio	0.05M KOH mL.[a]	NH_3/ CH_3NH_2 mmol	NH_3/CH_3NH_2 yield %[c,d]
1[8]	ChCl/Urea 1:2	18.5	0.075	0.09
2[b]	Sorbitol/Urea 5.2:4	9.3	0.535	0.66
3	Urea	20	0.000	0
4[18]	Glucose/Urea/$CaCl_2$ 1.6:4:0.5	19	0.005	0.006
5	Glycerol/Urea 10:4	4.9	0.755	0.94
6[8]	ChCl/DMU 1:2	19.5	0.025	0.03
7	Glycerol/DMU 10:4	19.5	0.025	0.03
8	Sorbitol/DMU 5.2:4	19.3	0.035	0.04
9[18]	Fructose/Urea 3:2	18	0.100	0.12

[a] Theoretical volume of 0.05M KOH aqueous solution needed for complete neutralization of H_2SO_4 solution (10mL, 005M) is 20mL. [b]urea/sorbitol DES was previously prepared in this molar ratio in our laboratory. [c] Calculated as a percent from the theoretical yield of ammonia considering full urea decomposition. [d] The ammonia/CH_3NH_2 which may have remained dissolved in the DES is not taken into account and the actual yields are expected to be higher.

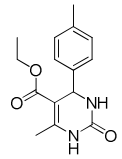
The obtained results were in agreement with our previous observation that the urea decomposition is enhanced in presence of poly alcohols. As it was expected, pure urea was complete stable at 80°C and no ammonia was detected (Table 3, entry 3). The highest amount of ammonia was observed in case of glycerol (Table 3, entry 5) and sorbitol (Table 3, entry 2), while only small amount was observed for ChCl (Table 2, entry 1). When carbohydrates such as glucose and fructose were used only minor amounts of ammonia were detected (Table 3, entries 4 and 9). However, after 7 hours at 80°C the colour of these DES turns brown, probably due to carbohydrates decomposition and formation of humins, which also should be taken into account when they are used as a reaction media at high temperatures. Switching from urea to dimethylurea DMU resulted in more stable DES and only traces of methylamine were observed, even with glycerol and sorbitol (Table 3, entries 7 and 8).

Experimental

General: All the reagents were purchased from Sigma-Aldrich or Merck and were used without further purification. The reaction evolution was followed by TLC using silica Merck Kieselgel 60 F254 plates, and revealed by ultraviolet light at 254 nm and 325 nm. NMR spectra were recorded at room temperature in a Bruker AMX 300 or Bruker AMX 400 using $CDCl_3$ or DMSO-d_6 as solvents. The MS spectra of the glycerol urea mixture (5:2 molar ratio) was recorded using Thermo Scientific High Resolution Magnetic Sector MS DFS by chemical ionization.

Preparation of Sorbitol-Urea DES: 13.96 g of urea and 49.8 g of sorbitol were mixed and stirred at 80°C for 3h till homogeneous liquid mixture was formed.

Ethyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**).[28]



5g of sorbitol/urea DES were placed in a round bottom flask then *p*-tolyl aldehyde (1mmol, 120mg), ethyl acetoacetate (1mmol, 130mg) and *p*-TsOH (0.2mmol, 34mg) were added and stirred overnight at 90°C. The reaction was dissolved in 10 mL of water. After complete dissolution, the product was extracted with ethyl acetate 2x25 mL. The organic phase was dried over Na_2SO_4, evaporated and the crude was purified with automatic flash chromatography machine -CombiFlash using gradient mixing of hexane and ethylacetate to give 260.4 mg (95%)

Reported M.p 170-172 °C; found: 171-172ºC.

The spectral data (^{1}H and ^{13}C NMR) is identical with the reported.[29]

^{1}H NMR (300 MHz, DMSO-d6) δ (ppm) 9.16 (s, 1H, NH), 7.68 (br s, 1H, NH), 7.12 (s,4H), 5.10 (d, 1H, J=3.3 Hz), 3.36 (q, 2H, J=7.1 Hz), 2.49 (s, 3H), 2.24 (s, 3H), d 1.10 (t, 3H, J=7.1 Hz)

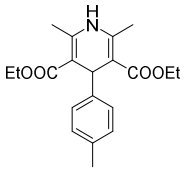
^{13}C NMR (100 MHz, DMSO-d6) δ (ppm), 166.3, 152.9, 148.9, 142.8, 137.3, 129.7, 126.8, 100.2, 59.9, 54.5, 21.4, 18.5, 14.8.

Synthesis of Nessler reagent: A saturated solution of $HgCl_2$ (~2.2g in 35 mL of distilled water) was added to a solution of 5g of KI in 5 mL of distilled water until the excess is indicated by the formation of a precipitate. Then 20mL of 5N NaOH were added and the mixture diluted to 100 mL with distilled water. The solution was left to settle and the clear liquid was draw off.

Nessler test: To a solution of 0.1g sorbitol/urea DES, urea or sorbitol in 4 mL of distilled water were added several drops of the Nessler reagent. The appearance of yellow colour was followed as a sign for the presence of ammonia.

General procedure for the synthesis of 1,4 dihydropyridine derivatives: 5g of sorbitol/urea DES were placed in a round bottom flask then 1mmol of the corresponding aromatic aldehyde and 2 mmol of ethyl acetoacetate were added and stirred overnight at 90°C. The reaction was dissolved in 10 mL of water. After complete dissolution, the product was extracted with ethyl acetate 2x25 mL. The organic phase was dried over Na_2SO_4, evaporated and the crude was purified with automatic flash chromatography machine (CombiFlash) using gradient mixing of hexane and ethyl acetate.

Diethyl 2,6-dimethyl-4-(p-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2**).[30]



Light yellow solid, yield: 140mg, 41%. Reported M.p: 136–137°C;[30] found: 140-142°C.

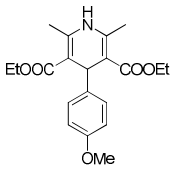
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.17 (d, J = 7.6 Hz, 2H), 7.01 (d, J = 7.6 Hz, 2H), 5.74 (s, 1H), 4.95 (s, 1H), 4.08 (q, J = 7.0 Hz, 4H), 2.31 (s, 6H), 2.27 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) δ 167.70, 144.89, 143.81, 135.50, 128.56, 127.83, 104.23, 59.70, 39.10, 21.05, 19.56, 14.26.

ESI-MS: calculated for $[C_{20}H_{25}NO_4 + H]^+$/z: 344.24; found: (M+H)/z: 344.15

IR (KBr, cm^{-1}): 3342.64 (NH), 2982.11 (Ar-H), 2936.77 (CH), 1693.65 (C=O).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**7a**).[31]



Light yellow solid, yield: 160mg, 48%. Reported M.p: 148–153°C;[31] found: 156-157°C.

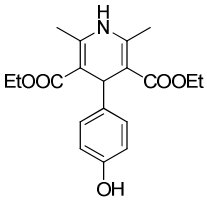
^{1}H NMR (400 MHz, CDCl3) δ (ppm) 7.19 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 5.62 (s, 1H,), 4.92 (s, 1H), 4.21 – 3.99 (m, 4H,), 3.75 (s, 3H,), 2.32 (s, 6H), 1.22 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, CDCl3) δ (ppm) 167.83, 158.00, 143.66, 140.46, 129.10, 113.31, 104.54, 59.84, 55.27, 38.86, 19.74, 14.41.

ESI-MS: calculated for $[C_{20}H_{25}NO_5 + H]^+$/z: 360.42; found: (M+H)/z: 360.08

IR (KBr, cm^{-1}): 3342.64 (NH), 2983.88 (Ar-H), 2956.87 (CH), 1689.64 (C=O).

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**7b**).[32]



Yellow solid, yield: 131mg, 38%. Reported M.p: 230-231°C;[32] found: 219-220°C.

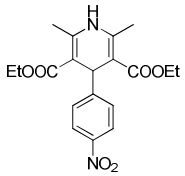
1H NMR (400 MHz, DMSO) δ (ppm) 9.07 (s, 1H), 8.70 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.57 (d, *J* = 8.5 Hz, 2H), 4.74 (s, 1H), 4.00 – 3.96 (m, 4H), 2.23 (s, 6H), 1.13 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ (ppm) 167.11, 155.44, 144.77, 138.92, 128.29, 114.52, 102.29, 58.89, 37.87, 18.21, 14.21

ESI-MS: calculated for $[C_{19}H_{23}NO_5 + H]^+$/z: 346.40; found: (M+H)/z: 346.02

IR (KBr, cm-1): 3346.50 (N-H), 2985.81 (Ar-H), 2937.59 (CH), 1662.64 (C=O), 1442.75 (C-OH).

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**7c**).[31]



Yellow solid, yield: 189mg, 50%. Reported M.p: 118–127°C;[31] found: 129-130°C.

^{1}H NMR (400 MHz, CDCl3) δ (ppm) 8.07 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 5.84 (s, 1H), 5.08 (s, 1H), 4.11 – 4.05 (m, *J* = 7.1, 3.1 Hz), 2.34 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, CDCl3) δ (ppm) 167.10, 155.14, 146.34, 144.70, 128.92, 123.30, 103.18, 60.02, 40.14, 19.65, 14.27.

ESI-MS: calculated for $[C_{19}H_{22}N_2O_6 + H]^+$/z: 375.40, found: (M+H)/z: 375.06

IR (KBr, cm 1): 3319.49 (NH), 2926.01 (Ar-H), 2852.72 (CH), 1701.22 (C=O).

Conclusions

The reported unusual basicity of urea based DES[17, 19, 23] can be explained by the urea decomposition and liberation of ammonia, even at lower than the expected temperatures. The presence of ammonia was detected during unexpected formation of dihydropyridines *via* Hantzsch synthesis in sorbitol/urea DES and further confirmed with Nesstler reagent tests. The formation of ammonia was not caused by simple thermal urea decomposition and was enhanced in presence of poly alcohols *via* the formation of cyclic carbonates. Neat or mono alcohols solutions of urea were observed to be completely stable under heating up to 80°C for at least 7h. ChCl was found to be an exception and although being mono alcohol, low rate of urea decomposition was also detected at 80°C for 12h. DMU based DES were more stable since DMU is less prompt to react with alcohols forming carbonates and insignificant amounts of methylamine were detected. Besides the extremely useful and high potential of DES clearly demonstrated for different applications after the pioneer discovery of Abbott *et al.,*[8-10] this study provides some guidelines about their use for long time under high temperature in which for some specific DES combination,

namely urea/polyalcohols occurs some ammonia liberation. These observations could be of importance for applications using urea based DES in different areas such as organic synthesis since, as we have shown, ammonia could be a catalyst or a reactive nucleophile in organic reactions performed in this reaction media.

Acknowledgements

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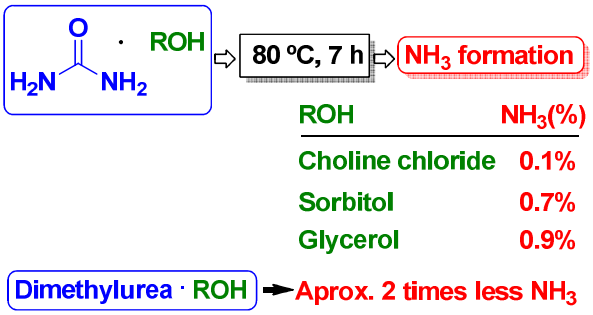
Deep eutectic mixtures/solvents (DES)



Some decomposition occurs below 100°C for urea based deep eutectic mixtures/solvents (DES) liberating ammonia and is enhanced for diols by formation of carbonates.