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First evidence of cyclodextrin inclusion complexes in a deep eutectic solvent

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Abstract

Cyclodextrins (CD) inclusion complexes are generally studied in aqueous solutions or more rarely in the presence of cosolvent. In this study, we investigated the ability of CD to retain their host-guest properties in deep eutectic solvent (DES). Five cyclodextrins were solubilized in choline chloride:urea (ChCl:U) and these new solutions were characterized by measuring the viscosity and density of the different mixture. The heat of dissolution of β-CD in ChCl:U was measured by calorimetry. The dissolution process is exothermic meaning that the interaction between DES and CD are favorable (enthalpy of dissolution of – 23.3 J/g). The ability of CDs to form inclusion complexes with various guests in ChCl:U was demonstrated using two different methods: UV-Visible spectroscopy and static headspace gas chromatography. On one hand, the experimental data obtained from the complexation between methyl orange and CDs follows the theoretical fitted curved for 1:1 inclusion complex. On the other hand, the observed volatility reductions of four volatile organic compounds in different mixture of DES/CDs were correlated to the CD/guest formation constant values determined in water. These results will certainly enlarge the application of CD in the DES field.

Keywords: cyclodextrin, deep eutectic solvent, formation constant, inclusion complexes.

Introduction

Supramolecular chemistry is based on the creation of noncovalent bonds between chemical species, leading to the formation of well-organized structures[1]. These bonds are based on relatively weak intermolecular interactions which are often reversible and influenced by the microscopic structure. Cyclodextrins (CDs) play an important role on the advancement of supramolecular chemistry as they are the most widely used host molecular structures[2]. CDs are cyclic oligosaccharides obtained from the enzymatic degradation of starch. Native CDs consist of six (α-CD), seven (β-CD) or eight (γ-CD) glucopyranose units, bound by α-(1–4) linkages forming a truncated conical structure with different cavity size (Figure 1).

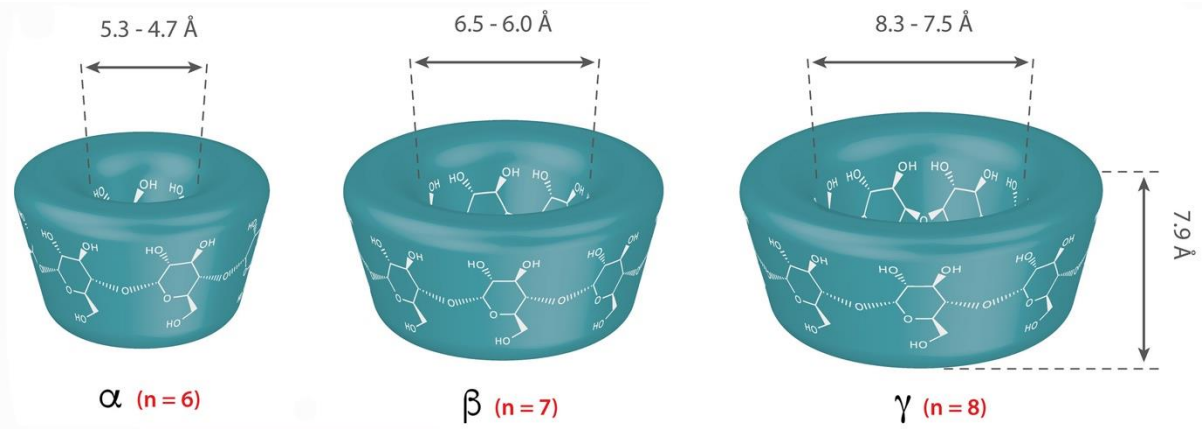


Figure 1: Representation of the 3 native cyclodextrins

The hydrophobic cavity of CDs, associated to their hydrophilic outer surface, enable them to encapsulate hydrophobic compounds to form host-guest inclusion complexes. The formation of inclusion complexes with CDs has been extensively studied in aqueous solution. Different factors affecting the complexation were assessed, as the temperature or the ionic strength. Few studies were nevertheless performed in the presence of co-solvents, like ethanol or DMSO, whose presence generally causes a decrease in the strength of the inclusion complex. To the best of our knowledge, only one example of inclusion complexes in non-aqueous media is reported in the literature, between β-CD and steroids in pure DMSO[3].

Deep eutectic solvents (DESs) recently emerged as a new generation of sustainable solvents[4]. DESs are mixtures of two compounds that form a eutectic point at a temperature well below that of the ideal mixture. To facilitate their use as solvents, it is convenient that the melting temperature is also below that of the temperature at which the dissolution process takes place (for example, room temperature) and, for practical reasons, at a range of compositions near the eutectic composition. The most popular DESs are generally mixtures of a hydrogen bond donor and a hydrogen bond acceptor, that at precise ratios lead to homogenous mixtures[5]. Because the DESs normally include salts, they can have similar physicochemical properties to those of ionic liquids but they are often cheaper, surely easier to produce and often prepared from mixing naturally occurring compounds, less toxic and mostly biodegradable. DESs have been used as extractant for organic and biologically active compounds, as media for organic, catalytic or enzymatic reactions or for solubilizing CO_2, SO_2 and volatile organic compounds[6,7].

Few studies have combined the use of CDs and DESs. The low-melting mixture of β-CD with N-methylurea has been recently used as reaction media for Suzuki–Miyaura and Heck reactions[8] and CD mixed with N,N'-dimethyl urea was taken as media for Tsuji-Trost and hydroformylation reactions[9,10]. The extraction of polyphenols using DESs and β-CD was reported, but no correlation could be made between the additions of β-CD to various DESs and the yield of extracted polyphenols[11]. Furthermore, a recent work investigated the solubilization of natives CDs and cucurbit*[n]*urils in choline chloride:urea (1:2) DES. It was found that the solubility of natives CDs was significantly enhanced in choline chloride:urea compared to aqueous environment[12]. These authors also studied the interaction of methylviologen with CB[7], CB[8], β- and γ-CD in the DES solution. However, except for cucurbituril derivatives, they were not able to prove complexation by titration methods using analytical techniques.

We recently patented the use of DES as absorbent for volatile organic compounds (VOC)[13]. In this patent, the effect of CD on the solubilization of some VOC in ChCl:U DES was also

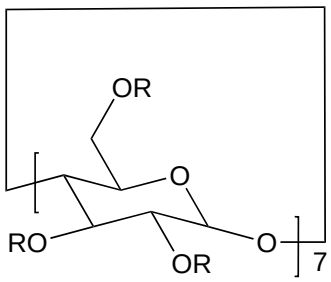
investigated by using static headspace gas-chromatography. We could observe a variation on the solubilisation capacities of the DES depending on the amount of added CDs. Therefore, in this work, we have investigated the effect of CD addition in mixtures of choline chloride and urea, at or near the eutectic point. Titration experiments were realized by UV-Vis spectrophotometry, in the case of methyl orange, and by static-headspace gas chromatography (SH-GC) in the case of volatile compounds (toluene, dichloromethane, limonene and *tert*-butylcyclohexane). The viscosity as well as density of these new solvents of CD in the DES were also determined and the dissoulution of β-CD in ChCl:U was investigated using dissolution calorimetry.

Materials and methods

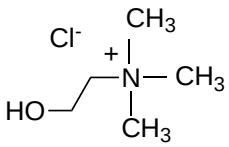
Materials

Choline chloride (98%), urea (99%), methyl orange (85%), toluene (99.8%), dichloromethane (99.8%), limonene (99%) and *tert*-butylcyclohexane (99%) were purchased from Sigma-Aldrich. α-CD, β-CD and γ-CD were provided by Wacker-Chemie (Lyon, France), low methylated-β-CD (CRYSMEB, DS = 4.9) and (HP-β-CD, DS= 5.6) were provided by Roquette Frères (Lestrem, France). Choline chloride was dried by placing it in an oven at 60°C for 2 weeks prior to use, the other compounds were used as received.

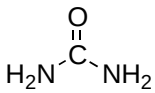
The structures of the compounds used in this work are depicted in Figure 2.



CRYSMEB (DS 4.9): R= -H or $-CH_3$
HP-b-CD (DS 5.6): R= -H or $-CH_2-CH(OH)-CH_3$



Choline chloride



Urea

Figure 2: Structure of the compounds used in this work.

Preparation of the Choline chloride:urea DES

Accurate amounts of dried choline chloride (ChCl) and urea (U) were mixed with respect to the molar ratio ChCl:U 1:2. The mixtures prepared are listed in Table S1 of the Supplementary Information (SI). Each mixture was stirred at 80°C until a transparent homogenous solution was obtained. All samples were kept in sealed containers to avoid contact with atmospheric humidity that may affect the physical properties of the DES. The water content of each DES and of each solution of CD in the DES was determined using a coulometric Karl Fisher titrator (Mettler Toledo DL31). The values are listed in Table S2 and vary between 0.06 %w/w for ChCl:U to 4.18 %w/w for the solution of 10% CRYSMEB in ChCl:U.

Density and viscosity measurements

Density was measured using a U shaped vibrating-tube densimeter (Anton Paar, model DMA 5000 M) operating in a static mode. All measurements were performed at atmospheric pressure and at temperatures between 303.15 K and 333.15 K. The factory calibration was used and verified before and after each measurement with air and tri distilled degassed water. The DMA 5000 densimeter performs an analysis with an estimated uncertainty in density and temperature of ±0.1 kg m^{-3} and ±0.001°C, respectively. The device has a built-in correction for liquids with a viscosity up to 700 mPa s, as in the present case.

The viscosity of the DES and of the CD solutions was measured using a falling-ball-based microviscosimeter (Lovis 2000 M/ME from Anton Paar) at atmospheric pressure and in the temperature range 303.15−333.15 K. The temperature was controlled to within 0.005 K and measured with an accuracy better than 0.02 K. A capillary tube of 1.8 mm diameter, previously

calibrated as the function of temperature and angle of measurement with reference oils, was used for the measurements. The overall uncertainty on the viscosity was estimated to be 2%.

Dissolution calorimetry

The heat of dissolution of the CDs in the DES was measured using a 25 mL precision solution semi-adiabatic (*i.e.* isoperibol) solution calorimeter housed in a TAM III thermostat from TA instruments. The experiments were performed at 60˚C and the quantities of CD and DES were determined gravimetrically. The experimental procedure described previously[14,15] was followed but special care was taken when filling the glass ampoule with dried samples of CD in order to avoid contamination with atmospheric water. The glass ampoule was flame-sealed before introduction in the calorimeter.

The experimental data obtained during the dissolution of cyclodextrine in the DES was adjusted, as explained before[14,15] to the equation:

$$T(t) = \frac{n_0 \Delta H}{C_p} \frac{t_c}{t_c - t_d} \left(e^{-t/t_c} - e^{-t/t_d} \right) + T_\infty$$

Where τ_d and τ_c are the characteristic times of dissolution and of thermal relaxation of the calorimeter, respectively; T_∞ is the temperature when the calorimeter is in equilibrium with its surrounding thermostat; C_p is the heat capacity of the calorimeter and ΔH is the enthalpy of dissolution. The values of τ_c and C_p are determined from a calibration measurement performed in the solution after dissolution using a heat pulse from an electrical heater.

UV-visible spectroscopy

Spectra were recorded using a Perkin Elmer Lambda 2S double beam spectrometer and a quartz cell with optical path length of 10 mm at 298 K. Spectra were recorded between 510 and 520 nm. The control of temperature was achieved by the use of a thermostated bath linked to the cell holder (accuracy: ±0.1 °C). An algorithmic treatment was applied to the first derivatives of UV spectra in order to avoid any spectral influence of diffraction phenomena [16].

A stock solution of ChCl:U with an adequate amount of methyl orange (MO) was prepared and then divided into aliquots. Different amount of β-CD and HP-β-CD (0.5, 1, 1.5, 2, 2.5% *wt*) were then added to the vials. The vials were sealed and kept under stirring for 24 hour at 30°C to ensure homogenization of the samples.

Static headspace gas chromatography (SH-GC)

A precise amount of ChCl:U was placed in 20 mL headspace vials. α-CD, β-CD,γ-CD, HP-β-CD and CRYSMEB were added to the DES at 2, 4, 6 and 10% (*wt*). After homogenization of the solutions, an equal amount of the volatile compounds (toluene, dichloromethane, limonene and *tert*-butylcyclohexane) was added to the samples. The sample were then kept under stirring for 24 hour to reach the equilibrium at 30°C. Then, the samples were left for 120 min in the headspace oven at 30°C prior to the analysis. All measurements were carried out with an Agilent G1888 headspace sampler coupled to a Perkin Elmer Autosystem XL gas chromatography equipped with a flame ionization detector and a DB624 column using nitrogen as carrier vector. The gas chromatography column temperature was set at 40˚C, 80˚C, 120˚C and 160˚C for dichloromethane, toluene, limonene and *tert*-butylcyclohexane, respectively. The transfer line temperature was set at 250˚C.

Results and discussion

DES characterization

The density experimental values for ChCl:U and for the different ChCl:U:CD solutions are reported on Table S2 of the SI. The values were adjusted to appropriate polynomial functions of the temperature and the parameters of the fits are listed in Table S3 of the SI. The values measured herein are compared with those published in the literature on Table S4 of the SI at normal pressure and at temperatures from 303.15 to 333.15 K. The deviations encountered are always lower than 0.1%, the larger differences being found at 303.15 K between our data

and those of Abbott *et al.*[5] and those of Leron and Li[17] which are 0.09% higher than those reported herein.

The ChCl:U:CD solutions are denser than the pure DES at all the temperatures studied, the density increasing when the concentration of CD increases. The same behavior is found at the higher temperature studied, 333.15 K, with the differences between the densities of the 2% and 10% solutions becoming less important.

The viscosity values are listed in Table S4 of the SI. The difference in the viscosity values between DES1 and DES7 can be explained by the different amounts of water measured for the two samples of DES (Table S1 of the SI). In light of these values, the addition of CD to the DES does not lead to a significant difference in the viscosity of the liquid solution except for the 10% solutions of γ-CD and HP-β-CD for which a significant increase of the viscosity is observed at the temperatures covered. For the solution of 10% of CRYSMEB a lower viscosity was measured in the temperature range covered.

Dissolution calorimetry

The temperature profile obtained when a sample of β-CD was dissolved in the DES is presented in Figure 3. The first peak corresponds to the CD dissolution and the second concerns the response of the calorimeter to a 2 J heat pulse thus serving to calibrate the heat capacity and relaxation tie of the apparatus.

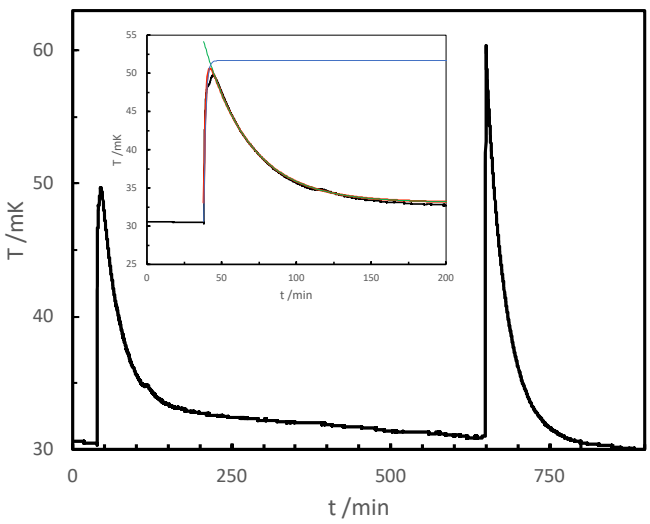


Figure 3: Temperature profile of the solution calorimeter when a 290.880 mg sample of β-CD is dissolved at 60°C in 27.947 mL of DES6. The insert represents the detail of the fitting used to determine the enthalpy of dissolution (details given in the Supplementary Information table S7).

It is observed that the dissolution of β-CD in the DES is an exothermic process with an enthalpy of dissolution of – 23.3 J/g (26.4 kJ/mol). Being an exothermic process means that the interactions between the DES and the CD are highly favorable but also means that an increase in temperature does not facilitate the dissolution, at least not in terms of the thermodynamics of the process.

Titration experiments

The formation of an inclusion complexes could be investigated in aqueous solution by titration experiments using various analytical techniques (NMR, UV-Visible, HS-GC, ITC) [18–20]. In the case of UV-visible spectroscopy, we could observe the variation of the guest absorbance in presence of increasing CD concentrations. In order to investigate if the different CD are able to form inclusion complexes when dissolved in DES, we follow the variation of the area of the second derivatives of MO in DES in the absence and in the presence of different percentage of β-CD and HP-β-CD (Figure 4).

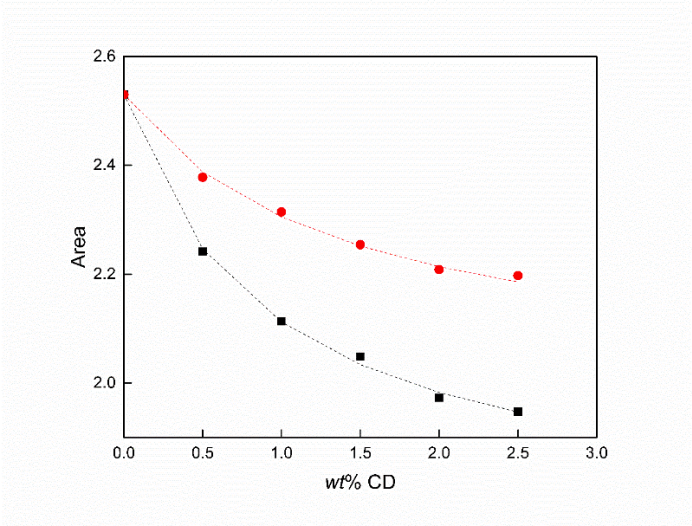


Figure 4: Variation of the area of the second derivative of methyl orange for different percentage of β-CD(●) and HP-β-CD(■), with the theoretical fitted curves (dashed lines) for a 1:1 inclusion complex.

As can be seen from Figure 4, the addition of CD to ChCl:U lead to a variation of the absorbance of MO. Moreover, this variation is in good agreement with the theoretical variation of this absorbance in the case of a 1:1 inclusion complex[16]. This agreement between experimental points and theoretical curves supports the assumption that a 1:1 inclusion complex is formed between MO and CD dissolved in a ChCl:U DES. These results observed at low CD percentage support the role of CD as a cage molecule for MO.

Assuming the existence of an inclusion complex, the formation constant (K_f) of MO with both CDs in ChCl:U could be determined using an algorithmic treatment[16]**Erreur ! Signet non défini.** The values listed in Table 2 are in good correlation with the values obtained in water, with the K_f value of HP-β-CD/MO inclusion complex being higher than the one with β-CD[18]. However, these K_f values are much lower in ChCl:U than in water. This could be due to the fact that MO is more soluble in ChCl:U than in water. Indeed, the main driving force of the formation of an inclusion complex is the better affinity of the guest for the hydrophobic CD cavity compared to the solvent, usually water. In addition, one cannot exclude that the cyclodextrin cavity is less available within the DES than in water, as each DES component could act as a potential competitor for inclusion.

Table 2: Formation constant (M^{-1}) of CD/MO in water and ChCl:U.

	H_2O	ChCl:U
β-CD	2500[18]	70
HP-β-CD	5373[18]	141

The effect of the addition of CDs, at higher concentrations than for the UV-vis study, to the ChCl:U DES on the retention of various volatile compounds was followed using SH-GC. We chose guest molecules with a large range of K_f value in water (see Table 3), in order to evaluate if the selectivity of the CDs is maintained when dissolved in the ChCl:U DES. This selectivity is mainly due to the steric complementarity of the CD and guest, inclusion complexes being stronger when there is a good geometrical complementarity between the guest and the CD cavity [19].

Table 3: Formation constant (M^{-1}) obtained for the various inclusion complexes in water.

	α-CD	β-CD	γ-CD	HP-β-CD	CRYSMEB
Dichloromethane	21[21]	9[21]	-	10[21]	9[21]
Toluene	38[22]	142[22]	33[22]	163[22]	165[22]
tert-Butylcyclohexane	248	4092[23]	18	2036[23]**Erreur ! Signet non défini.**	5577
Limonene	1289[24]	3162[24]	116[24]	2787[24]**Erreur ! Signet non défini.**	3668[24]**Erreur ! Signet non défini.**

The addition of CD to an aqueous VOC aqueous solution lead to a decrease of the chromatographic peak area as a function of CD concentration[25]. The peak area being relative to the concentration of the compound in the gaseous phase, a decrease of the area is linked to a higher solubilization of the volatile compound in solution. If such a phenomena is observed in ChCl:U, this could be related to the formation of an inclusion complex in the eutectic solvent.

As can be seen in Figure 5, the obtained chromatographic peak area decrease in the presence of CDs excepted for dichloromethane. In this case (Figure 5a), the presence of CDs tends toward a slight increase of the chromatographic peak area. This results can be related to the low K_f values of CD/dichloromethane inclusion complexes in water (Table 3). Indeed, dichloromethane is a small molecule that did not filled entirely the CD cavity[21].

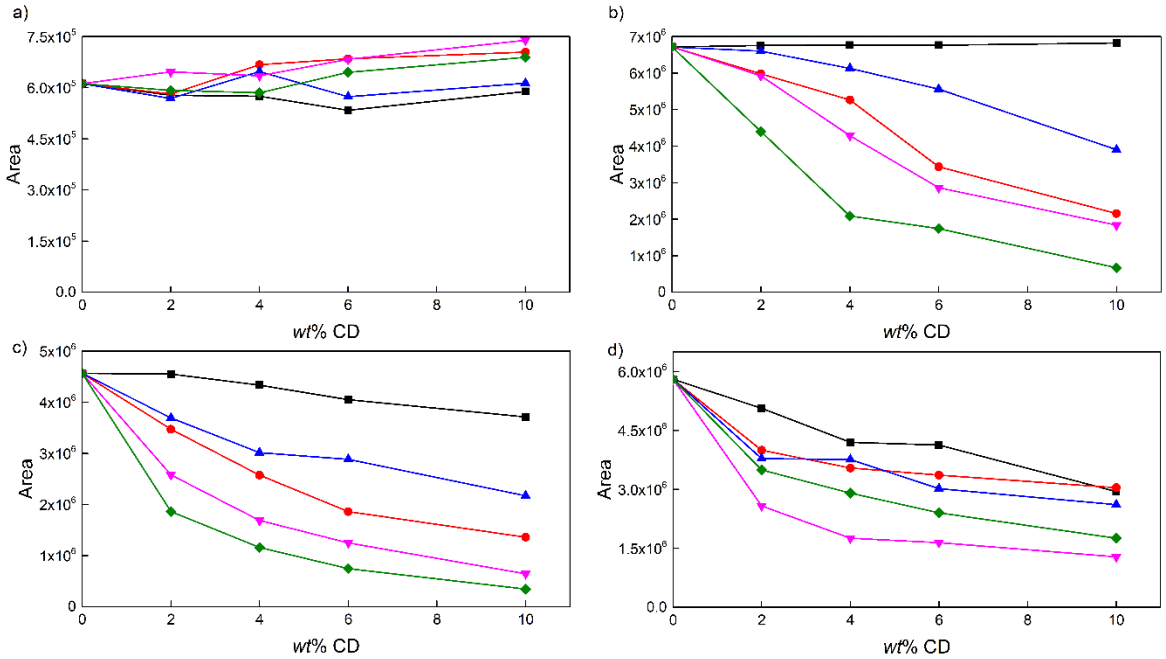


Figure 5: Variation of the chromatographic peak area in the presence of various amount of CD for (a) dichloromethane, (b) *tert*-butylcyclohexane, (c) limonene and (d) toluene.(■α-CD; ●β-CD;▲ γ-CD; ▼ HP-β-CD;◆ CRYSMEB).

For *tert*-butylcyclohexane (Figure 5b), limonene (Figure 5c) and toluene (Figure 5d) we can clearly distinguish the selectivity between the different types of CD. The effect of β-CD and its

derivatives in ChCl:U is more pronounced than for α-CD and γ-CD. This effect could be related to the greater K_f values of these compounds with β-CD and its derivatives compared to α-CD and γ-CD in water (Table 3). Indeed, the size of the CD cavity is to small for these guest and the one of CD too large to have a good filling of the cavity[23].

It is noteworthy to mention, that a sample containing 10% (*wt*%) of methyl α-D-glucopyranose was also prepared in order to determine if the solubilization properties of the CD solutions could be due to a “sugar effect” or to the presence of the cavity. No variation in the peak area was observed for this sample for all the studied volatile compounds. This result highlights the role of the cavity in the absorption enhancement of the volatile compounds, and consequently the formation of inclusion complexes between the CD and the guest molecule in the ChCl:U DES.

Finally, we reported the maximum volatility reduction obtained in water and in DES in Figure 6. As can be seen, a good correlation is obtained between these values, thus supporting that the solubilizing mechanisms of VOC induced by the presence of CD are analogous in water and DES. Such result constitutes another proof that CDs are able to form inclusion complexes within the ChCl:U DES.

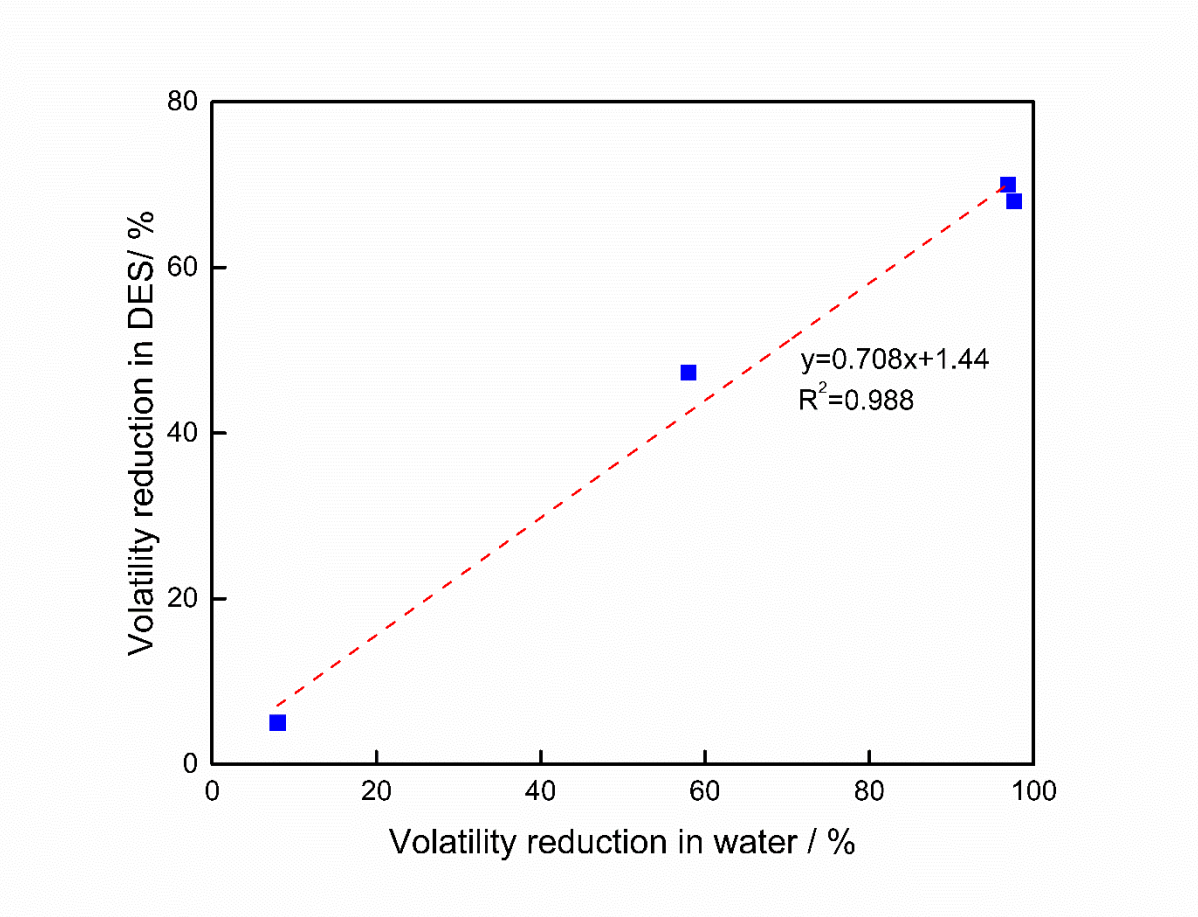


Figure 6: Correlation between the volatility reduction obtained in DES and in water in the case of β-CD ([β-CD]=0.01M)

McCune *et al*. [12] postulate that the enhanced solubility of natives CDs in ChCl:U results from the ability of the hydroxyl groups on the exterior of the CD to interact with the hydrogen-bonded network of the DES, which results in incorporation of the CDs within the bulk-liquid structure. In this paper, we demonstrated that CDs, although interacting with the DES components, retain their complexation properties in ChCl:U as shown through UV-Vis spectroscopy and static-headspace gas chromatography. Moreover, the selectivity of the different CDs towards various guest molecules is also maintained in these solvents.

4. Conclusion

In this paper, the three natives CDs (α-, β-, γ-CD) and two modified β-CD (HP-β-CD, CRYSMEB) were solubilized in ChCl:U DES. The physico-chemical properties of the solvents were characterized by measuring their density, and viscosity and the heat of dissolution was measured for one of the native CDs. The dissolution of β-CD in the DES is exothermic, meaning that an increase of temperature is not thermodynamically favorable. Raising the temperature increases the fluidity of the DES thus facilitating mass transport and leading to a faster dissolution of CD.

The complexation ability of CDs in ChCl:U DES was investigated for the first time using 2 different methods. Results obtained at low cyclodextrin concentrations for MO by the titration method using UV-Vis measurements are in good agreement with the theoretical fitted curves for a 1:1 inclusion complex. Furthermore, the solubilisation of four volatile organic compounds was measured by SH-GC. The variation of the chromatographic peak area, related to the amount of solubilized compound, as a function of CD amount is in good agreement with their relative affinity for CDs in water. The selectivity of CDs towards the guests is preserved in ChCl:U, underlining the formation of inclusion complexes between CD and guest in ChCl:U. The use of ChCl:U as solubilizing agent for dissolving high amount of CDs compared to water, especially in the case of β-CD, associated to a maintained molecular recognition could expand the applications of CDs in many fields.

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in the measurement of the density and viscosity of the solutions studied in this work and Prof. A. Padua for his help with the fit of the calorimetric data.

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