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Solubility and solvation features of native cyclodextrins in 1-Ethyl-3-methylimidazolium Acetate.

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Abstract.

The comprehension of the mechanism entailing efficient solvation of cyclodextrins (CD) by green solvents is of great relevance to boost environmentally sustainable usages of smart supramolecular systems. Here, 1-ethyl-3-methylimidazolium acetate, an ecofriendly ionic liquid (IL), is considered as an excellent solvent for native CDs. This IL efficiently dissolves up to 40 %wt. β - and γ -CD already at ambient temperature and x-ray scattering indicates that CDs do not tend to detrimental flocculation under these drastic concentration conditions. Simulation techniques reveal the intimate mechanism of CD solvation by the ionic species: while the strong hydrogen bonding acceptor acetate anion interacts with CD's hydroxyl groups, the imidazolium cation efficiently solvates the hydrophobic CD walls via dispersive interactions, thus hampering CD's hydrophobic driven flocking. Overall the amphiphilic nature of the proposed IL provides an excellent solvation environment for CDs, through the synergic action of its components.

Keywords: ionic liquids; dissolution mechanism; hydrophobic solvation; cyclodextrin; emerging task specific solvents; sustainability

1. Introduction.

The most common, native cyclodextrins (CDs), α -, β - and γ -CD, are doughnut-shaped, cyclic oligo-carbohydrates, bearing 6, 7 and 8 D-glucoses bound by $\alpha(1-4)$ bonds, respectively (Saenger et al., 1998; Szejtli, 1998). Their hydrophobic conical cavity can selectively host, in a reversible way, a variety of apolar guests, otherwise poorly soluble in aqueous or polar solvents. Native CDs offer high biocompatibility and availability and a huge realm of opportunities in supramolecular chemistry, food and pharmaceutical industry, separation and extraction technologies (Alsaiee et al., 2016; Armstrong et al., 1999; Brewster & Loftsson, 2007; Li et al., 2022; Loftsson & Brewster, 2010, 2012; Szejtli, 1998; Tian et al., 2021; Uekama et al., 1998). However, despite their inherently amphiphilic nature, due to the hydrophilic -OH groups at the upper and lower rims, native CDs (especially β -CD) show limited solubility in common solvents, including water (Jozwiakowski & Connors, 1985; Sabadini et al., 2006). Accordingly, large efforts are paid to the conception and development of solvents with higher efficiency in solvating CDs, yet mitigating the environmental impact.

In this scenario, ionic liquids (IL) represent a huge opportunity (Earle & Seddon, 2000; Plechkova & Seddon, 2008; Rogers & Seddon, 2003; Triolo et al., 2007; Weingärtner, 2008; Welton, 1999). Since the first reports on their capability to dissolve cellulose (Swatloski et al., 2002; Wang et al., 2012), ILs, which are composed solely of ionic species, emerged as impressive solvents for carbohydrates (Carneiro et al., 2013; Fukaya et al., 2008; E. R. E. Hassan et al., 2015; E. S. R. E. Hassan et al., 2013; Liu et al., 2010; Teles et al., 2016; Youngs et al., 2011). Hydrophilic ILs can dissolve CDs in large quantities: the solvation is thermodynamically unfavourable, it is entropically favoured and driven by enthalpy (Rogalski et al., 2013; Zheng et al., 2010). Yet, the mechanism behind CD dissolution in ILs has only marginally been investigated (Gonsior et al., 2010; Hou et al., 2018; Yu et al., 2008). The potentially detrimental CD aggregation in ILs at high concentrations is entirely unexplored and the role of the complex interplay between hydrogen bonding (HB) and dispersive interactions in solvating CDs remains largely unsettled. Here we intend to assess the remarkable capability of 1-ethyl-3-methylimidazolium acetate ([C2mim][AcO]) in dissolving α -, β - and γ -CDs. We hypothesise that the combination of acetate anion, with excellent HB capability, and imidazolium-based cation, with a well-known amphiphilic nature, is an excellent choice for an IL to effectively solvate natural CDs. We expect that this peculiar IL will thoroughly dissolve CDs with no occurrence of detrimental flocking; furthermore, we expect to detect a

specific solvation mechanism at atomistic level with a different role played by the hydrophilic anion and the amphiphilic cation, with the latter inhibiting the hydrophobic clustering of CDs. A major limitation in exploiting ILs for carbohydrates processing is the separation of the final product from solvent: in this respect, supercritical CO₂ has been recently proposed as an efficient method to separate carbohydrates dissolved in [C2mim][AcO] (Barber et al., 2013), thus paving the way for eco-sustainable, efficient processing of CDs in this IL.

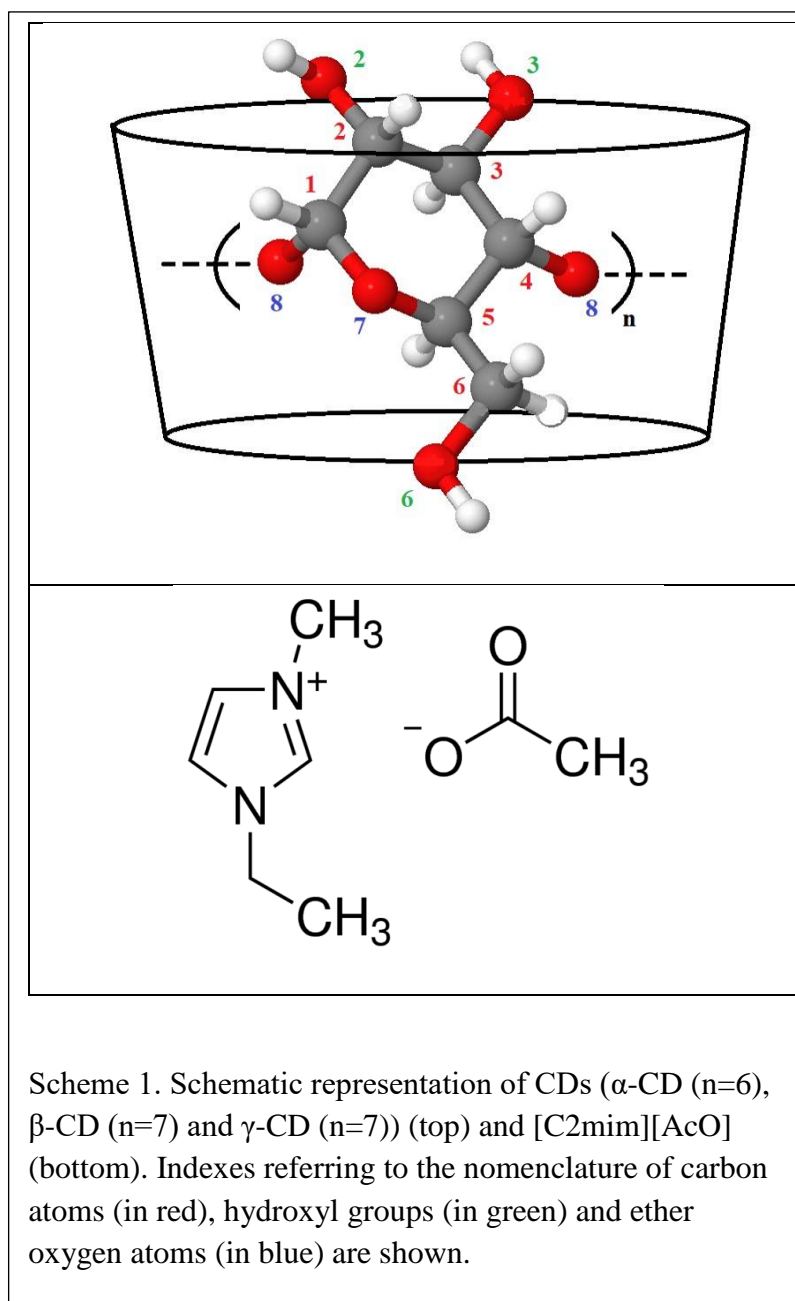
2. Methods.

2.1. Experimental Section.

2.1.1 Samples.

α -CD (99.3 %), β -CD (98.6 %) and γ -CD (99.3 %) were CYCLOLAB products (see Scheme 1).

They were kept at 60°C for one day before solution preparation.



1-Ethyl-3-methylimidazolium Acetate ([C2mim][AcO]) was a Iolitec product (>98%). It was dried at 50 °C under high vacuum for 24 hours and then stored under dry nitrogen, before solution preparation. Mixtures for X-ray scattering experiments were prepared with dry [C2mim][AcO] by weight, inside a dry-box. Subsequently, the mixtures were mixed at 50°C for 1 hour and then left to reach room temperature (ca. 20°C), where they are homogeneous.

2.1.2 Solubility characterization.

Approximately 0.5 g of binary mixtures were prepared in closed glass vials by adding [C2mim][AcO] and each CD at a given composition ratio, under inert atmosphere. The mixtures were left under constant stirring for one hour,

at the desired temperature (± 0.1 °C) in a thermostated water bath, Julabo F12. At the presence of residual solid, temperature was increased by 1 °C and the system was again monitored for full solvation. Solubility was considered complete when naked eye inspection did not allow the detection of residual solid CD.

2.1.3 SAXS measurements.

Small Angle X-ray Scattering (SAXS) measurements were performed at the SAXS Lab Sapienza with a Xeuss 2.0 Q-Xoom system (Xenocs SA, Sassenage, France), equipped with a micro-focus Genix 3D X-ray source ($\lambda = 0.1542$ nm) and a two-dimensional Pilatus3 R 300K detector.

Measurements cover the Q range: $0.04 \text{ \AA}^{-1} < Q < 0.6 \text{ \AA}^{-1}$. Samples were loaded into disposable quartz capillaries with nominal thickness 1.0 mm and sealed with hot glue. Measurements were conducted at ambient temperature (ca. 20°C) on x-CDs (x= α , β , γ) mixtures at concentration ~1 mol. % (corresponding to 65-90 mg/mL, depending on the x-CD). Additional details are provided in the ESI.

Measurements were also collected at the Swing beamline at the Soleil synchrotron. In this case we measured different x-CDs (x= α , β , γ) solutions at various concentrations (up to 800 mg/mL for β – CD) and temperatures (between 10 and 90°C). Additional details are provided in the ESI.

Similarly to our recent study on β -CD solvation in deep eutectic solvents (Triolo et al., 2020), fitting of the SAXS data was done using the SASView software (M. Doucet et al. SasView Version 4.2, Zenodo, 10.5281/zenodo.1412041). Solvent and instrumental background corrected S(Q) data were modelled assuming a core-shell sphere model to account for isolated, isotropically oriented x-CD molecules. Additional details are provided in the ESI.

2.2 Computational Details

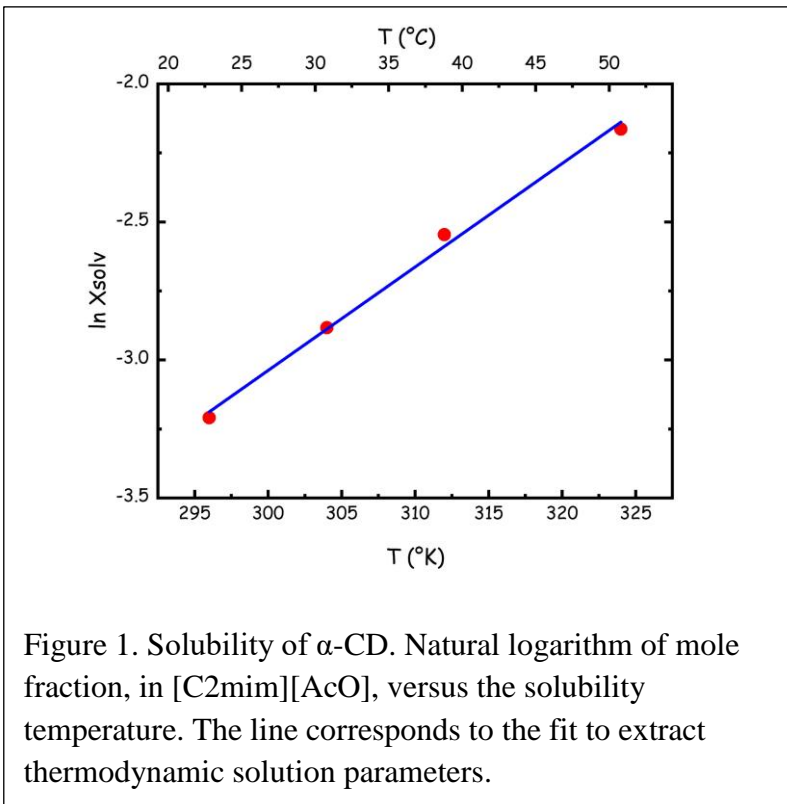
Molecular Dynamics (MD) simulations were performed using the GROMACS 5.1.1 package. (Hess et al., 2008; Van Der Spoel et al., 2005). Bonded and non-bonded parameters for x-CD and 1-ethyl-3-methylimidazolium acetate ([C2mim][AcO]) were described using an all-atoms potential. For [C2mim][AcO] we used an OPLS force field (Canongia Lopes et al., 2004; Canongia Lopes & Pádua, 2012; Jorgensen et al., 1996); for x-CDs we used the q4-MD force field (Cézard et al., 2011; Gebhardt et al., 2018; Zhang et al., 2012).

Simulations were performed using a cubic box of 500 ion pairs (500 [C2mim], 500 [AcO]) and 10 x-CD units (c=2 % mol., equivalent to ca. 150 mg_{x-CD}/mL_{IL}); scaled partial charges (80% of the original ones) were used for the IL and periodic boundary conditions were applied. Simulations were conducted at 323 K.

Analysis were conducted using the TRAVIS software (Brehm et al., 2020; Brehm & Kirchner, 2011; Hollóczki et al., 2015). Full details are provided in the ESI.

3. Results & Discussion.

[C2mim][AcO] turns out to be a very good solvent for α -CDs. At 15 °C (room temperature), we could characterize samples with concentration 270, 1000 and 1500 mg_{CD}/mL_{IL}, for α -, β -, γ -CD, respectively. Samples with concentrations 370, 110 and 2000 mg_{CD}/mL_{IL} for α -, β -, γ -CD, respectively, are biphasic at the same temperature. For comparison, corresponding solubilities in water at 25°C are 129.5, 18.4 and 249.2 mg_{CD}/mL_{water}, respectively (Sabadini et al., 2006). Here a distinction between α -CD and β -, γ -CDs is required. While for α -CD, one could easily distinguish between biphasic and homogeneous mixtures and hence determine the solubility dependence from temperature, on the other hand, for the case of β - and γ -CDs this was not possible, likely due to the



high viscosity of concentrated solutions that hindered crystallization and did not allow the detection of separated/homogeneous transitions. High viscosity was reported for methylated β -CD dissolved in [C2mim][AcO], highlighting the formation of a temperature responsive gel (Gonsior et al., 2010).

Accordingly, we limited our exploration of the solubility features only to α -CD solutions.

Natural logarithm of the mixture

compositions (in molar fraction), $\ln x_{\text{solv}}$, and the corresponding solubility temperature are plotted in

Figure 1. These data were used to extract Gibbs free energy of solution, ΔG_{solv} , enthalpy of solution, ΔH_{solv} and entropy of solution, ΔS_{solv} , by the following equations:

$$\Delta G_{\text{solv}} = -RT \ln(x_{\text{solv}});$$

$$\Delta H_{\text{solv}} = RT^2 d(\ln x_{\text{solv}})/dT;$$

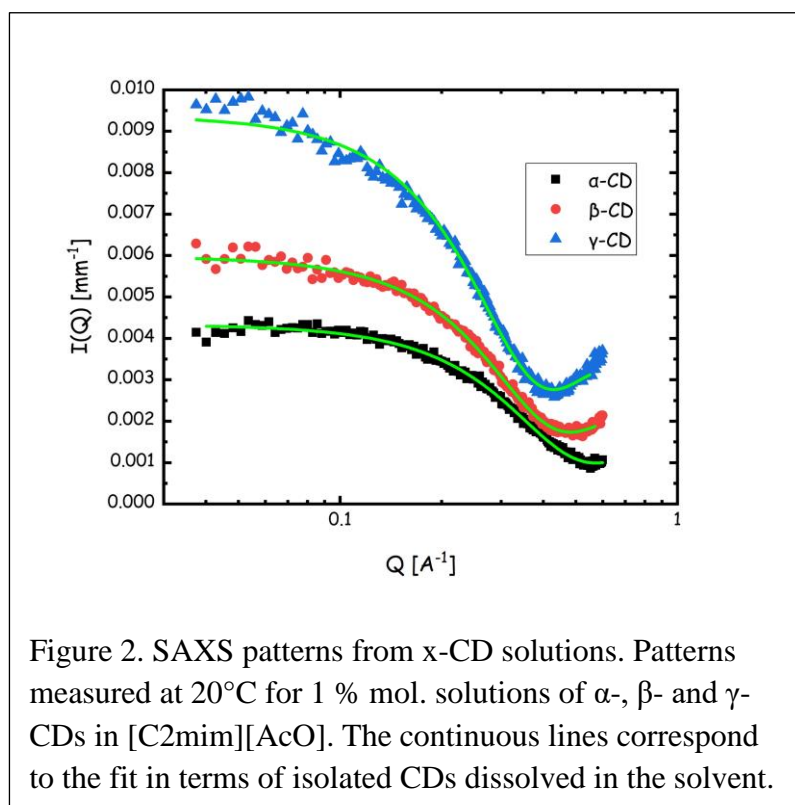
$$\Delta S_{\text{solv}} = \Delta H_{\text{solv}} - \Delta G_{\text{solv}}.$$

Fitting the experimental data in **Figure 1**, one extracts data reported in **Table 1**.

T [°K]	ΔG_{solv} [kJ/mol]	ΔH_{solv} [kJ/mol]	$T\Delta S_{\text{solv}}$ [kJ/mol]
296.2	7.8	27.3	19.4
304.2	7.3	28.8	21.5
312.2	6.7	30.3	23.6
324.2	5.8	32.7	26.9

Table 1. Solution thermodynamic parameters for α -CD dissolved in [C2mim][AcO] at different temperatures.

Values for ΔG_{solv} , ΔH_{solv} and $T\Delta S_{\text{solv}}$ are positive; in particular $\Delta G_{\text{solv}} > 0$ and $\Delta H_{\text{solv}} > T\Delta S_{\text{solv}}$, thus



indicating that intermolecular interactions between α -CD and ionic species are weaker than inter-ionic ones and the solvation process is endothermic, with an increase in solubility with temperature and a major role played by enthalpic effects to solvation. This behaviour is similar to the one observed for β -CD in other ionic liquids (Zheng et al., 2010) and in different monosaccharides dissolved in other ILs (Padaszyński et al., 2013; Teles et al., 2016).

Selected mixtures of α -, β - and γ -CD in [C2mim][AcO], have been characterised by SAXS, in order to probe the potential degree of aggregation of CDs in the chosen solvent. The clustering of CDs in water and other media has been reported (Coleman et al., 1992; Miyajima et al., 1983; Szente et al., 1998) and acknowledged as a potentially detrimental effects (e.g. poorly soluble aggregates and unwished drug-CD interactions) (Loftsson et al., 2019). CD aggregation in water is a debated issue: NMR studies (A. J.M. Valente et al., 2017; Artur J M Valente et al., 2015) do not prompt for the

existence of CDs aggregates in water and SAXS/SANS experiments conducted on β - and γ -CDs in dilute solutions in water did not show evidences of aggregates up to 6 and 42.9 mg/mL, respectively. (Kusmin et al., 2008) However, light scattering probed CD aggregates even in dilute solutions in water (12 mM) (Bonini et al., 2006; González-Gaitano et al., 2002). Herein, we are exploring a concentration range of the order of 65 to 87 mg/mL, depending on the CD (corresponding to 1 % mol.). **Figure 2** reports the experimental SAXS patterns from x-CDs in [C2mim][AcO] at 1 % mol. concentration, at ca. 20°C, together with their fit in term of the above described monodisperse, hard sphere, core-shell model. The model nicely accounts for the scattering features, without the requirement for consideration of CD aggregates. We also characterised more concentrated solutions (up to 800 mg/mL for the most concentrated mixtures with β -CD), in the temperature range 10-90 °C. The corresponding SAXS data are reported in **Figures ESI-1** and indicate that there are no CD flocking effects over the probed concentration/temperature range. Accordingly, we can validate the hypothesis that [C2mim][AcO] behaves as an excellent solvent for x-CDs, hindering their aggregation even at very high concentration. Such an important conclusion prompts for exploitation of CDs in the present solvent (e.g. for separation or host-guest opportunities) and calls for the assessment of the fundamental solvation features of [C2mim][AcO] towards x-CDs.

MD simulations were developed for the three mixtures (c=2 %mol., equivalent to ca. 150 mg_{x-CD}/mL_{IL}) at 323 K, ensuring that equilibrium is achieved and reliable statistical robustness is achieved across the simulations. Additionally, a comparable quality MD simulation was conducted for neat [C2mim][AcO], at the same conditions. This simulation led to an equilibrium value for density of 1.068 g/cc at 323 K, (experimental value: 1.0834 g/cc (Oliveira et al., 2015)). We also derived the X-ray and neutron scattering static structure factor (**Figure ESI-2**). Neutron data for different selectively deuterated samples appear in good agreement with published data (Bowron et al., 2010), further validating the structural information extracted from our simulation for neat [C2mim][AcO].

We will now extract structural details at atomistic level on the nature of x-CDs' solvation by [C2mim][AcO]. Overall, the simulated binary systems showed, in agreement with experimental findings, a homogeneous distribution of CDs in the simulation box, without evidences of phase separation, as shown in **Figure ESI-3**.

A preliminary picture of x-CDs solvation can be extracted by inspecting pair distribution functions (pdf) of cation/anion – CD centers of mass (CoM) (**Figure 3**) accounting for the distribution of cation (**Figure 3 left**) and anion (**Figure 3 right**) CoM around the reference CD's CoM. Therein the intramolecular distribution functions of the reference CD atoms are also shown, in order to help

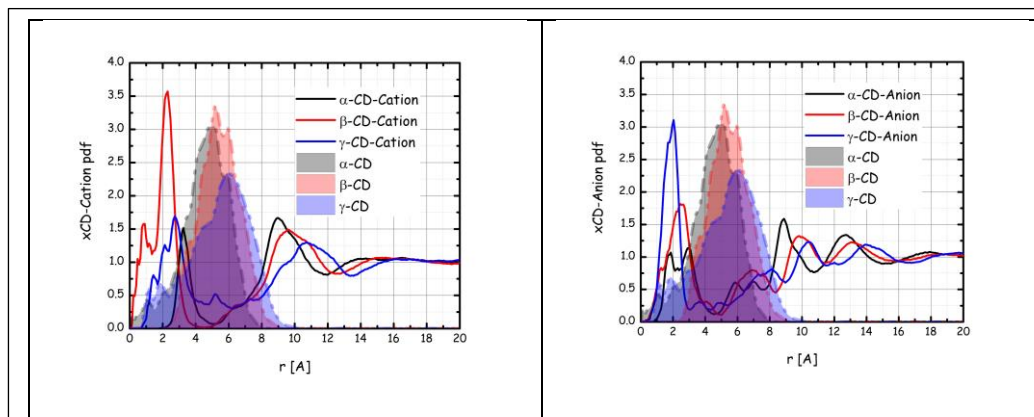


Figure 3. Distribution of ionic species around reference CDs. Pair distribution functions referring to the centers of mass of x-CD (x=α-, β- and γ-) and either Cation (left) and Anion (right) in mixtures of x-CDs dissolved in [C2mim][AcO]. The shadowed area refer to the intramolecular distribution functions of atoms belonging to the same x-CD.

rationalise distributions inside and outside the CD cavity. Both ionic species appear inside the x-CDs, as indicated by the curves in **Figure 3** for $r < 4 \text{ \AA}$: by integration of the

pdfs, in **Figure ESI-4**, one can extract that on average 0.6, 1 and 0.9 cations and 0.65, 0.85 and 0.7 anions are at a distance $r < 4 \text{ \AA}$ from the α-, β- and γ-CD CoMs, respectively. Inspection of spatial distributions shows that imidazolium rings tend to occupy the access to the CDs, while anions can locate inside the CD structure.

3.1 Organization of ionic species inside x-CD.

Figure 3 qualitatively indicates a different organization of anion and cation species inside x-CDs: in order to better clarify this issue, we monitored in detail the orientation of such species with respect to the x-CD axis. Concerning the cation, we monitored the orientation of the imidazolium ring (IR) perpendicular axis with respect to the CD axis (angle θ); concerning the anion, the orientation of the C-C direction was monitored with respect to the CD axis (angle φ). **Figures 4** and **5** respectively show the combined distribution functions (cdf) built up for such studies. In **Figures 4 a-c**, the abscissas report the distance between the x-CD CoM and the IR center, d , while the ordinate axis reports the angles between the CD axis and the axis normal to the IR. Therein, different hot lobes can be detected, corresponding to enhanced probability for the corresponding IR organization inside the CD. The preferred cation organizations inside the x-CD (hottest lobes in **Figures 4 a-c**,

highlighted with a black circle) are shown in **Figures 4 d-f**, for the three x-CDs, respectively. Other specific cation organizations, corresponding to other weaker lobes, are reported in the ESI (**Figure**

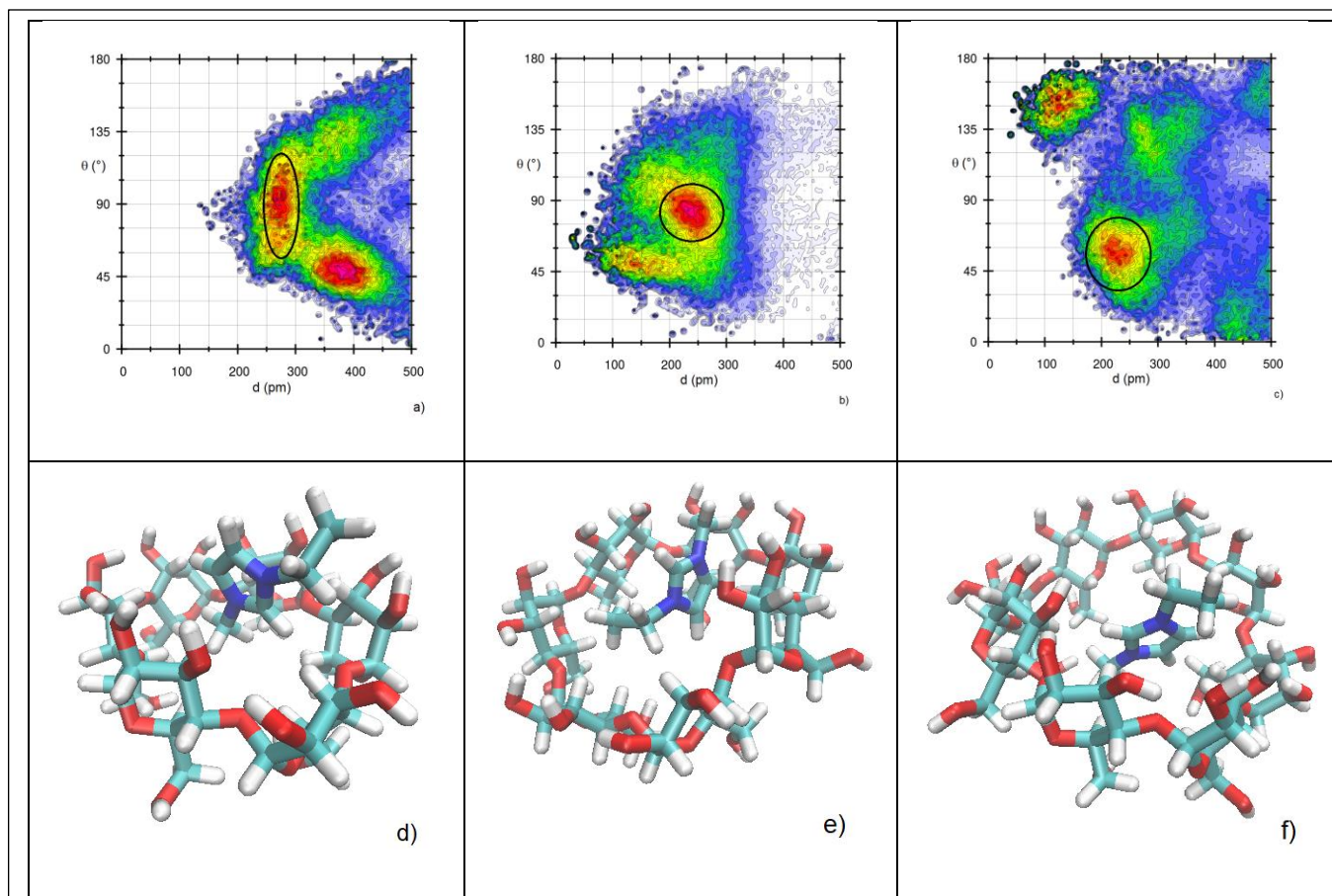


Figure 4. Organization of cations inside CDs. Combined distribution functions of the distance imidazolium ring-CD CoM, d , and orientation of the ring with respect to the CD axis, θ , for α -, β - and γ -CD (a-c), respectively). Structural organization of the ring inside the CD corresponding to the most common occurrence for α -, β - and γ -CD (d-f), respectively).

ESI-5). For α -CD (**Figure 4 d**) and β -CD (**Figure 4 e**), the IR does not enter the CD cavity, but rather locates at the largest CD rim, with the ring axis perpendicular to the CD axis. The other (weaker) hot lobes for α -CD and β -CD correspond (case II in **Figures ESI-5** and **ESI-6**, respectively) to an IR located at larger distance from the α -CD center with a tilted orientation and an IR located well inside the β -CD cavity, with a tilted orientation, the difference between the two CDs likely due to their different sizes.

In the case of γ -CD (**Figure 4 f**), the IR lies well inside the CD cavity, close to its larger rim, with an angle of ca. 60° between the CD axis and the imidazolium one. There are two more (weaker) hot lobes in the case of γ -CD. One (case II in **Figure ESI-7**) corresponds to an IR lying inside the CD cavity at the large rim of the cavity; an even weaker spot (case III in **Figure ESI-7**) corresponds to

another conformation with a highly deformed CD geometry and the IR lying again flat at the larger rim.

Overall, the most IR common locations tend to be at the entrance of the α -CD, rather than inside the α -CD, although evidences are found of the presence of IR inside β - and γ -CD (lobes at distance shorter than 1.5 Å). We remind that reports exist mentioning inclusion of IR inside α -CDs, in aqueous solutions (Gao et al., 2005).

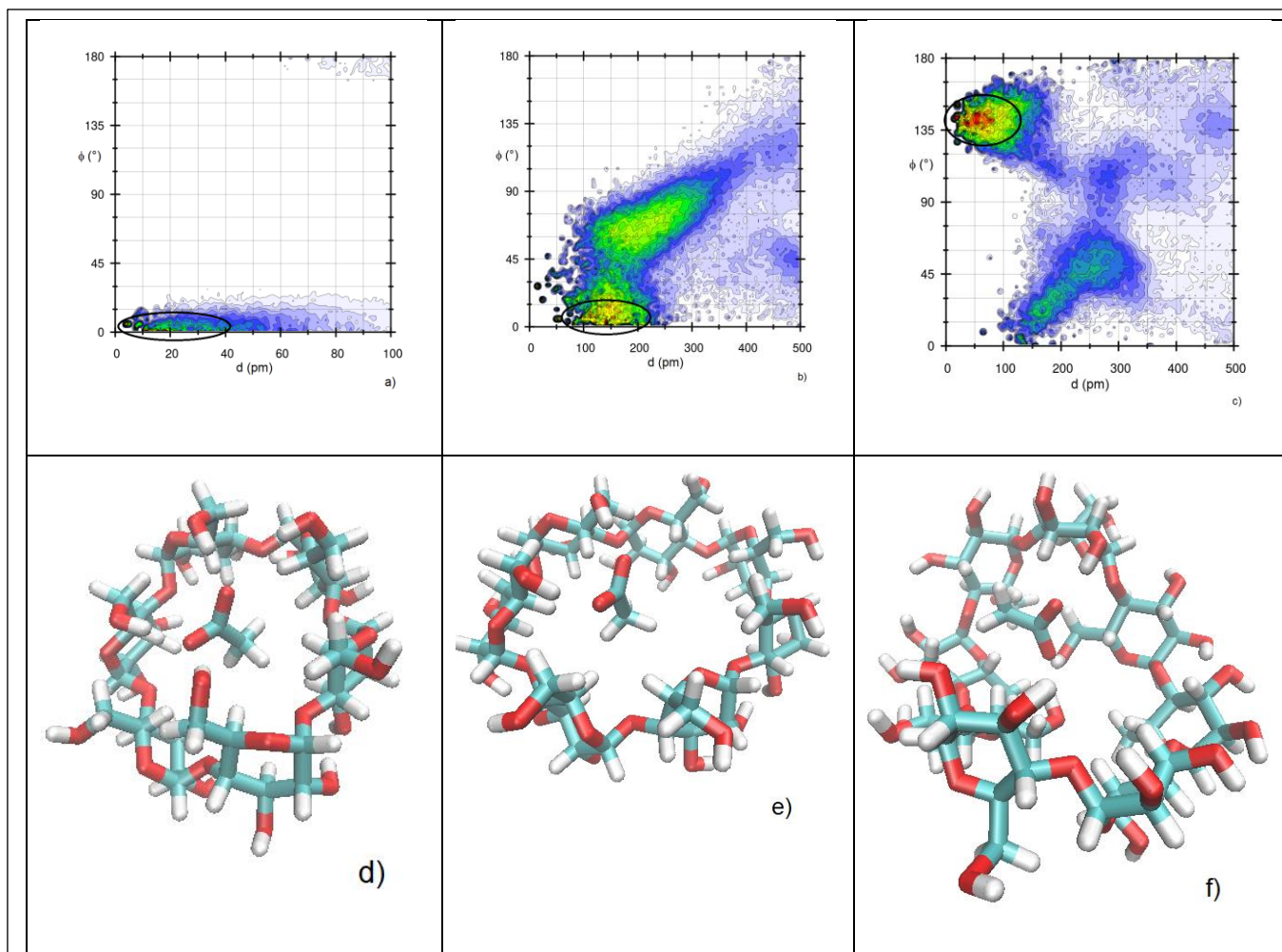


Figure 5. Organization of anions inside CDs. Combined distribution functions of the distance anion-CD CoMs, d , and orientation of the anion C-C bond with respect to the CD axis, ϕ , for α -, β - and γ -CD (a-c), respectively). Structural organization of the anion inside the CD corresponding to the most common occurrence for α -, β - and γ -CD (d-f), respectively).

Anions can better approach the interior part of CDs, especially through HB interactions with the CD's hydroxyl groups. In **Figures 5 a– f**, we show the cdf of anions approaching CD's center and the corresponding most common configurations.

It appears that in the case of α -CD (**Figure 5 a and d**), a single hot lobe can be detected corresponding to an anion very close to the CD center and with the anion axis C-C parallel to the CD axis. In the case of β - and γ -CD, two hot spots can be detected. In the former case, the most

common configuration involves an anion fully aligned with CD axis, with the oxygens involved in HB interactions with CD's hydroxyl groups; the weaker spot corresponds (case II in **Figure ESI-8**) to an anion lying at the narrower rim.

In γ -CD, both organizations involve an anion interaction through HB with the hydroxyl groups of the larger rim, but the irregular shape of the CD does not allow a clear picture on the anion localization (see also case II in **Figure ESI-9**). It clearly emerges that for the three CDs, anions are always detected close to the CD center, with a strong role of HB in driving this organization.

3.2 Organization of ionic species outside x-CD.

The steric hindrance of x-CD's walls prevents accommodation of species at distance between ca. 4 and 8 Å from the x-CD CoM, as shown in **Figure 3**. Outside of the x-CD, one distinct cation solvation shell can be identified extending up to 12-13 Å. On the other hand, anions tend to develop a much better structured solvation pattern around the reference x-CD. They first directly interact with the CD's hydroxyl groups, via HB, leading to a weak peak centred at ca. 6-8 Å. They then develop two solvation shells that extend up to 15-16 Å. Cation and anion solvation shells are sequentially distanced from the reference x-CD, according to the order imparted by the x-CD size. The first solvation shell is composed by both cations and anions that distribute close to the CDs external surface. The anion distribution superimposes, in a jigsaw fashion, to the cation one, thus maintaining local electro-neutrality. However, one can notice that cations tend to approach the hydrophobic external CD walls at a closer distance and correspondingly anions try to find a location where to distribute. Such a situation reflects a specific feature of imidazolium based ILs in solvating mono, oligo and poly-saccharides: while anions such as acetate mostly interact with carbohydrates through coulombic and HB mediated interactions, imidazolium cations engage in a substantial dispersive interaction with carbohydrates. In order to explore this feature, we decomposed the MD derived interaction energies of x-CDs with cations and anions in terms of coulombic and dispersive contributions. These data are shown in **Table 2**. Anions show a very large coulombic contribution (ca. -10,000 kJ/mol) and a much more limited dispersive contribution (ca. -700 kJ/mol).

Species	Coulombic Interaction Energy (kJ/mol)			Dispersive Interaction Energy (kJ/mol)		
	α -CD	β -CD	γ -CD	α -CD	β -CD	γ -CD
CD-cation	-413.4	-204.7	-462.7	-3,760.9	-4,565.9	-4,771.0
CD-anion	-8,977.7	-10,935.3	-11,744.0	-676.0	-625.4	-778.7

Table 2. Interaction energies (kJ/mol) between x-CDs and cation ([C2mim]) and anion ([AcO]) species.

In the case of cations, the situation is the opposite: we detect a limited (ca. -350 kJ/mol) coulombic contribution and a much stronger (ca. 4,000 kJ/mol) dispersive one. Such a peculiar nature of interactions between ions and carbohydrates has been observed for other ILs dissolving e.g. cellulose (Liu et al., 2010; Rabideau et al., 2014). These studies highlight the major role played by anions in stabilising the solvated carbohydrate via coulombic interactions, with only a minor role played by coulombic interactions involving cations. The latter, however, show a very significant dispersive contribution to the carbohydrate solvation. Considering the inherently amphiphilic nature of CDs chemical structure (Connors, 1997), such dispersive interactions play a fundamental role for the efficient solvation of CD's hydrophobic portion. In order to highlight this effect we monitored

the orientation of imidazolium rings surrounding a reference β -CD. In **Figure 6a**, we show a

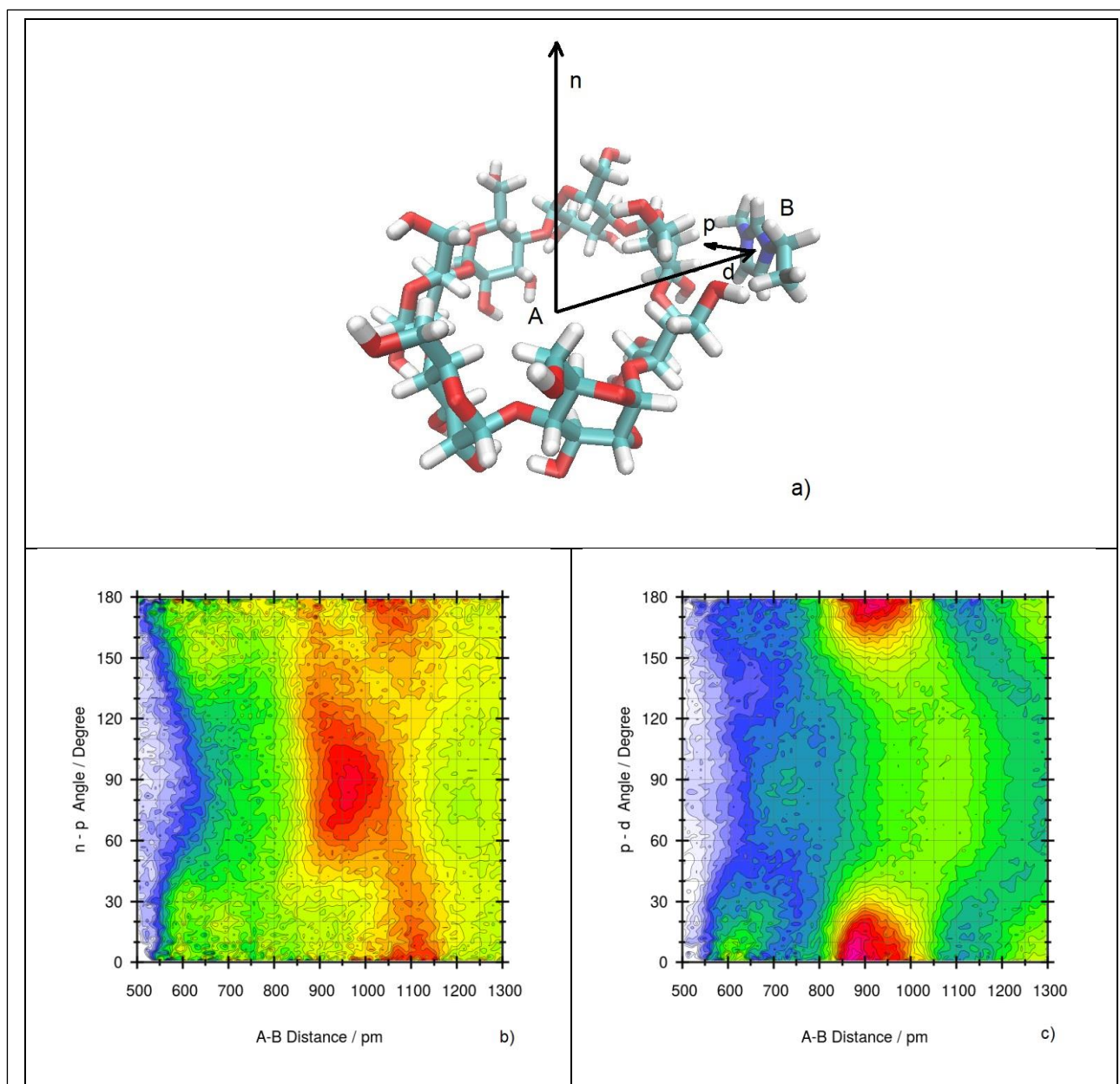


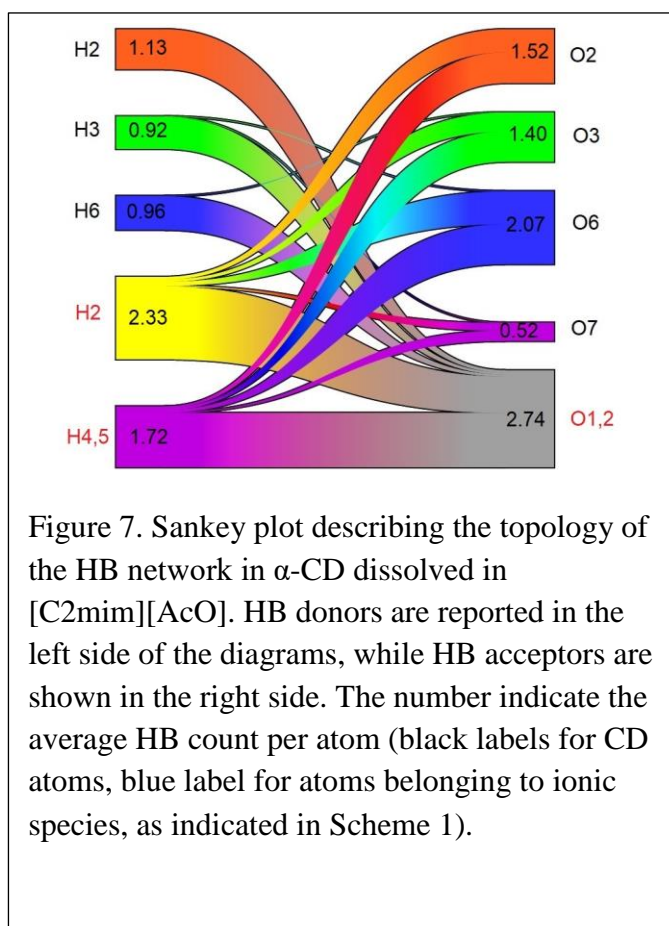
Figure 6. Hydrophobic solvation of CD by imidazolium ring. a) common spatial organization of imidazolium ring belonging to the first solvation shell around reference CD. Corresponding CDF describing in abscissa the distance ring – CD COMs and in ordinate the orientation of the ring with respect to: b) CD axis and c) vector connecting ring – CD COMs.

reference CD solvated by a representative cation belonging to the first IR solvation layer. It emerges that of IRs belonging to the first solvating shell (A-B distance ~ 9.5 Å) tend to distribute around CD's hydrophobic walls in a highly organised way. In particular we detect that the ring normal axis, p , is perpendicular to the CD axis, n , (see **Figure 6b**) and parallel to the line connecting CD and IR centers, d , (see **Figure 6c**), so to maximise dispersive interactions. Such a strongly oriented cation layer is responsible for the hydrophobic solvation of CD, while anions surrounding CD walls will merely occupy available space among cations, in a jigsaw fashion, to maintain electro-neutrality. It

follows that such a highly ordered cation layer around CDs eventually hinders the hydrophobic-driven flocculation of CDs in this medium.

3.3 HB interactions between ionic species and α -CD.

HB is the main interaction occurring between CDs and ILs, in particular [C2mim][AcO]. In **Figure ESI-10**, selected pdfs referring to these interactions for the case of α -CDs are shown. Each CD's hydroxyl hydrogen is coordinated by approximately one acetate anion, through a short ($r_{O-H} \sim 1.75$ Å) and linear ($O-H \cdots O_{\text{acetate}} > 165^\circ$) HB. Other correlations involving acidic cation's protons (such as the H2 in the imidazolium ring) and CD's oxygen atoms are characterised by longer distances and are only weak HBs. In order to better monitor the network of HB taking place in these systems, we report in **Figure 7** the Sankey diagram (Brehm et al., 2020) visualising the HB network



established between the different moieties present in the α -CD mixture (see figures for the other α -CDs in **Figure ESI-11**). Therein it clearly appears the major role played by the acetate anion in acting a HB acceptor. All the HB donors (belonging to either CD or imidazolium) are predominantly involved in HB interactions with the acetate oxygen atoms (O1, O2). Also CD's hydroxyl oxygens (O2, O3, O6) can efficiently act as HB acceptor from the imidazolium HB donor sites (H2, H4, H5).

Cations, on the other hand, interact with CDs mostly through dispersive interactions and engage HB interactions mostly with acetate anions. These observations lead us to state that the amphiphilic nature of

[C2mim][AcO] plays a fundamental role in determining the excellent solvation performances towards CDs. ILs with a strong HB acceptor anions, such as the acetate, develop a strong HB-mediated interaction with the CD hydrophilic portion. In turn, cations, such as imidazolium ones, succeed in efficiently solvate CD's hydrophobic portion, thus weakening hydrophobic interactions between neighbour CDs, even at high concentrations and correspondingly hamper CD aggregation.

4. Conclusion.

The fundamental role of the chemical nature of an eco-friendly ionic liquid in efficiently dissolving native CDs has been ascertained, using the complementarity of experimental and computational techniques. We show that 1-ethyl-3-methylimidazolium acetate behaves as an excellent solvent for α -, β - and γ -CD already at ambient temperature. X-ray scattering reveals that even at extreme concentrations, CD does not tend to flocculate and isolated CD are well solvated in the mixtures, thus enabling supramolecular chemistry applications. Simulations provide atomistic detail on the nature of the effective solvation mechanism of the IL towards CDs: while the acetate anion, a strong HB acceptor, solvates CD's hydrophilic moieties, on the other hand, the imidazolium cation develops stabilising dispersive interactions with the hydrophobic CD walls, thus effectively hampering CD's hydrophobic driven flocking. If one keeps in mind the recently proposed methods to separate carbohydrates from [C2mim][AcO], by means of sc-CO₂ treatment, these findings might provide useful guides for an eco-friendly development of supramolecular chemistry.

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VCREDIT:

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References

- Alsaiee, A., Smith, B. J., Xiao, L., Ling, Y., Helbling, D. E., & Dichtel, W. R. (2016). Rapid removal of organic micropollutants from water by a porous β -cyclodextrin polymer. *Nature*, *529*(7585), 190–194. <https://doi.org/10.1038/nature16185>
- Armstrong, D. W., He, L., & Liu, Y. S. (1999). Examination of ionic liquids and their interaction with molecules, when used as stationary phases in gas chromatography. *Analytical Chemistry*, *71*(17), 3873–3876. <https://doi.org/10.1021/ac990443p>
- Barber, P. S., Griggs, C. S., Gurau, G., Liu, Z., Li, S., Li, Z., Lu, X., Zhang, S., & Rogers, R. D. (2013). Coagulation of Chitin and Cellulose from 1-Ethyl-3-methylimidazolium Acetate Ionic-Liquid Solutions Using Carbon Dioxide. *Angewandte Chemie International Edition*, *52*(47), 12350–12353. <https://doi.org/10.1002/anie.201304604>
- Bonini, M., Rossi, S., Karlsson, G., Almgren, M., Lo Nostro, P., & Baglioni, P. (2006). Self-assembly of β -cyclodextrin in water. Part 1: Cryo-TEM and dynamic and static light scattering. *Langmuir*, *22*(4), 1478–1484. <https://doi.org/10.1021/la052878f>
- Bowron, D. T., D'Agostino, C., Gladden, L. F., Hardacre, C., Holbrey, J. D., Lagunas, M. C., McGregor, J., Mantle, M. D., Mullan, C. L., & Youngs, T. G. A. (2010). Structure and Dynamics of 1-Ethyl-3-methylimidazolium Acetate via Molecular Dynamics and Neutron Diffraction. *Journal of Physical Chemistry B*, *114*(23), 7760–7768. <https://doi.org/10.1021/jp102180q>
- Brehm, M., & Kirchner, B. (2011). TRAVIS - A Free Analyzer and Visualizer for Monte Carlo and Molecular Dynamics Trajectories. *Journal of Chemical Information and Modeling*, *51*(8), 2007–2023. <https://doi.org/10.1021/ci200217w>
- Brehm, M., Thomas, M., Gehrke, S., & Kirchner, B. (2020). TRAVIS—A free analyzer for trajectories from molecular simulation. *The Journal of Chemical Physics*, *152*(16), 164105. <https://doi.org/10.1063/5.0005078>
- Brewster, M. E., & Loftsson, T. (2007). Cyclodextrins as pharmaceutical solubilizers. *Advanced Drug Delivery Reviews*, *59*(7), 645–666. <https://doi.org/10.1016/j.addr.2007.05.012>
- Canongia Lopes, J. N., Deschamps, J., & Pádua, A. A. H. (2004). Modeling Ionic Liquids Using a Systematic All-Atom Force Field. *Journal of Physical Chemistry B*, *108*(6), 2038–2047. <https://doi.org/10.1021/jp0362133>
- Canongia Lopes, J. N., & Pádua, A. A. H. (2012). CL&P: A generic and systematic force field for ionic liquids modeling. In *Theoretical Chemistry Accounts* (Vol. 131, Issue 3, pp. 1–11). <https://doi.org/10.1007/s00214-012-1129-7>
- Carneiro, A. P., Rodríguez, O., & MacEdo, E. A. (2013). Fructose and glucose dissolution in ionic liquids: Solubility and thermodynamic modeling. *Industrial and Engineering Chemistry Research*, *52*(9), 3424–3435. <https://doi.org/10.1021/ie3024752>
- Cézard, C., Trivelli, X., Aubry, F., Djedaïni-Pilard, F., & Dupradeau, F. Y. (2011). Molecular dynamics studies of native and substituted cyclodextrins in different media: 1. Charge derivation and force field performances. *Physical Chemistry Chemical Physics*, *13*(33), 15103–15121. <https://doi.org/10.1039/c1cp20854c>
- Coleman, A. W., Nicolis, I., Keller, N., & Dalbiez, J. P. (1992). Aggregation of cyclodextrins: An explanation of the abnormal solubility of β -cyclodextrin. *Journal of Inclusion Phenomena and*

Molecular Recognition in Chemistry, 13(2), 139–143. <https://doi.org/10.1007/BF01053637>

- Connors, K. A. (1997). The stability of cyclodextrin complexes in solution. *Chemical Reviews*, 97(5), 1325–1357. <https://doi.org/10.1021/cr960371r>
- Earle, M. J., & Seddon, K. R. (2000). Ionic liquids. Green solvents for the future. *Pure and Applied Chemistry*, 72(7), 1391–1398. <https://doi.org/10.1351/pac200072071391>
- Fukaya, Y., Hayashi, K., Wada, M., & Ohno, H. (2008). Cellulose dissolution with polar ionic liquids under mild conditions: Required factors for anions. *Green Chemistry*, 10(1), 44–46. <https://doi.org/10.1039/b713289a>
- Gao, Y. A., Li, Z. H., Du, J. M., Han, B. X., Li, G. Z., Hou, W. G., Shen, D., Zheng, L. Q., & Zhang, G. Y. (2005). Preparation and characterization of inclusion complexes of β -cyclodextrin with ionic liquid. *Chemistry - A European Journal*, 11(20), 5875–5880. <https://doi.org/10.1002/chem.200500120>
- Gebhardt, J., Kleist, C., Jakobtorweihen, S., & Hansen, N. (2018). Validation and Comparison of Force Fields for Native Cyclodextrins in Aqueous Solution. *Journal of Physical Chemistry B*, 122(5), 1608–1626. <https://doi.org/10.1021/acs.jpcc.7b11808>
- Gonsior, N., Hetzer, M., Kulicke, W.-M. M., & Ritter, H. (2010). First studies on the influence of methylated β -cyclodextrin on the rheological behavior of 1-ethyl-3-methyl imidazolium acetate. *Journal of Physical Chemistry B*, 114(39), 12468–12472. <https://doi.org/10.1021/jp1036684>
- González-Gaitano, G., Rodríguez, P., Isasi, J. R., Fuentes, M., Tardajos, G., & Sánchez, M. (2002). The aggregation of cyclodextrins as studied by photon correlation spectroscopy. *Journal of Inclusion Phenomena*, 44(1–4), 101–105. <https://doi.org/10.1023/A:1023065823358>
- Hassan, E. R. E., Mutelet, F., & Bouroukba, M. (2015). Experimental and theoretical study of carbohydrate – ionic liquid interactions. *Carbohydrate Polymers*, 127, 316–324. <https://doi.org/10.1016/j.carbpol.2015.03.042>
- Hassan, E. S. R. E., Mutelet, F., Pontvianne, S., & Moïse, J. C. (2013). Studies on the dissolution of glucose in ionic liquids and extraction using the antisolvent method. *Environmental Science and Technology*, 47(6), 2809–2816. <https://doi.org/10.1021/es303884n>
- Hess, B., Kutzner, C., van der Spoel, D., & Lindahl, E. (2008). GROMACS 4: Algorithms for Highly Efficient, Load-Balanced, and Scalable Molecular Simulation. *Journal of Chemical Theory and Computation*, 4(3), 435–447. <https://doi.org/10.1021/ct700301q>
- Hollóczki, O., Macchiagodena, M., Weber, H., Thomas, M., Brehm, M., Stark, A., Russina, O., Triolo, A., & Kirchner, B. (2015). Triphasic Ionic-Liquid Mixtures: Fluorinated and Non-fluorinated Aprotic Ionic-Liquid Mixtures. *ChemPhysChem*, 16(15), 3325–3333. <https://doi.org/10.1002/cphc.201500473>
- Hou, X. D., Li, A. L., Lin, K. P., Wang, Y. Y., Kuang, Z. Y., & Cao, S. L. (2018). Insight into the structure-function relationships of deep eutectic solvents during rice straw pretreatment. *Bioresource Technology*, 249, 261–267. <https://doi.org/10.1016/j.biortech.2017.10.019>
- Jorgensen, W. L., Maxwell, D. S., & Tirado-Rives, J. (1996). Development and Testing of the OPLS All-Atom Force Field on Conformational Energetics and Properties of Organic Liquids. *Journal of the American Chemical Society*, 118(45), 11225–11236. <https://doi.org/10.1021/ja9621760>

- Jozwiakowski, M. J., & Connors, K. A. (1985). Aqueous solubility behavior of three cyclodextrins. *Carbohydrate Research*, 143(C), 51–59. [https://doi.org/10.1016/S0008-6215\(00\)90694-3](https://doi.org/10.1016/S0008-6215(00)90694-3)
- Kusmin, A., Lechner, R. E., Kammel, M., & Saenger, W. (2008). Native and methylated cyclodextrins with positive and negative solubility coefficients in water studied by SAXS and SANS. *Journal of Physical Chemistry B*, 112(41), 12888–12898. <https://doi.org/10.1021/jp802031w>
- Li, T., Guo, R., Zong, Q., & Ling, G. (2022). Application of molecular docking in elaborating molecular mechanisms and interactions of supramolecular cyclodextrin. *Carbohydrate Polymers*, 276, 118644. <https://doi.org/10.1016/j.carbpol.2021.118644>
- Liu, H., Sale, K. L., Holmes, B. M., Simmons, B. A., & Singh, S. (2010). Understanding the interactions of cellulose with ionic liquids: a molecular dynamics study. *The Journal of Physical Chemistry. B*, 114(12), 4293–4301. <https://doi.org/10.1021/jp9117437>
- Loftsson, T., & Brewster, M. E. (2010). Pharmaceutical applications of cyclodextrins: Basic science and product development. *Journal of Pharmacy and Pharmacology*, 62(11), 1607–1621. <https://doi.org/10.1111/j.2042-7158.2010.01030.x>
- Loftsson, T., & Brewster, M. E. (2012). Cyclodextrins as Functional Excipients: Methods to Enhance Complexation Efficiency. *Journal of Pharmaceutical Sciences*, 101(9), 3019–3032. <https://doi.org/10.1002/jps.23077>
- Loftsson, T., Saokham, P., & Sá Couto, A. R. (2019). Self-association of cyclodextrins and cyclodextrin complexes in aqueous solutions. *International Journal of Pharmaceutics*, 560(January), 228–234. <https://doi.org/10.1016/j.ijpharm.2019.02.004>
- Miyajima, K., Sawada, M., & Nakagaki, M. (1983). Viscosity B -Coefficients, Apparent Molar Volumes, and Activity Coefficients for α - and γ -Cyclodextrins in Aqueous Solutions. *Bulletin of the Chemical Society of Japan*, 56(12), 3556–3560. <https://doi.org/10.1246/bcsj.56.3556>
- Oliveira, F. S., Rebelo, L. P. N., & Marrucho, I. M. (2015). Influence of different inorganic salts on the ionicity and thermophysical properties of 1-ethyl-3-methylimidazolium acetate ionic liquid. *Journal of Chemical and Engineering Data*, 60(3), 781–789. <https://doi.org/10.1021/je5008857>
- Paduszyński, K., Okuniewski, M., & Domańska, U. (2013). “Sweet-in-Green” systems based on sugars and ionic liquids: New solubility data and thermodynamic analysis. *Industrial and Engineering Chemistry Research*, 52(51), 18482–18491. <https://doi.org/10.1021/ie4033186>
- Plechkova, N. V., & Seddon, K. R. (2008). Applications of ionic liquids in the chemical industry. *Chemical Society Reviews*, 37(1), 123–150. <https://doi.org/10.1039/b006677j>
- Rabideau, B. D., Agarwal, A., & Ismail, A. E. (2014). The role of the cation in the solvation of cellulose by imidazolium-based ionic liquids. *Journal of Physical Chemistry B*, 118(6), 1621–1629. <https://doi.org/10.1021/jp4115755>
- Rogalski, M., Modarelli, A., Magri, P., Mutelet, F., Grydziuszko, A., Wlazło, M., & Domańska, U. (2013). Physico-chemical properties and phase behavior of the ionic liquid- β -cyclodextrin complexes. *International Journal of Molecular Sciences*, 14(8), 16638–16655. <https://doi.org/10.3390/ijms140816638>
- Rogers, R. D., & Seddon, K. R. (2003). Ionic Liquids--Solvents of the Future? *Science*, 302(5646), 792–793. <https://doi.org/10.1126/science.1090313>

- Sabadini, E., Cosgrove, T., & Egídio, F. D. C. (2006). Solubility of cyclomaltooligosaccharides (cyclodextrins) in H₂O and D₂O: A comparative study. *Carbohydrate Research*, 341(2), 270–274. <https://doi.org/10.1016/j.carres.2005.11.004>
- Saenger, W., Jacob, J., Gessler, K., Steiner, T., Hoffmann, D., Sanbe, H., Koizumi, K., Smith, S. M., & Takaha, T. (1998). Structures of the common cyclodextrins and their larger analogues - beyond the doughnut. *Chemical Reviews*, 98(5), 1787–1802. <https://doi.org/10.1021/cr9700181>
- Swatloski, R. P., Spear, S. K., Holbrey, J. D., & Rogers, R. D. (2002). Dissolution of Cellulose with Ionic Liquids. *Journal of the American Chemical Society*, 124(18), 4974–4975. <https://doi.org/10.1021/ja025790m>
- Szejtli, J. (1998). Introduction and General Overview of Cyclodextrin Chemistry. *Chemical Reviews*, 98(5), 1743–1753. <https://doi.org/10.1021/cr970022c>
- Szente, E., Szejtli, J., & Kis, G. L. (1998). Spontaneous opalescence of aqueous γ -cyclodextrin solutions: Complex formation or self-aggregation? *Journal of Pharmaceutical Sciences*, 87(6), 778–781. <https://doi.org/10.1021/js9704341>
- Teles, A. R. R., Dinis, T. B. V., Capela, E. V., Santos, L. M. N. B. F., Pinho, S. P., Freire, M. G., & Coutinho, J. A. P. (2016). Solubility and solvation of monosaccharides in ionic liquids. *Physical Chemistry Chemical Physics*, 18(29), 19722–19730. <https://doi.org/10.1039/c6cp03495k>
- Tian, B., Liu, Y., & Liu, J. (2021). Smart stimuli-responsive drug delivery systems based on cyclodextrin : A review. *Carbohydrate Polymers*, 251(July 2020), 116871. <https://doi.org/10.1016/j.carbpol.2020.116871>
- Triolo, A., Lo Celso, F., & Russina, O. (2020). Structural Features of β -Cyclodextrin Solvation in the Deep Eutectic Solvent, Reline. *Journal of Physical Chemistry B*, 124(13), 2652–2660. <https://doi.org/10.1021/acs.jpcc.0c00876>
- Triolo, A., Russina, O., Bleif, H. J., & Di Cola, E. (2007). Nanoscale segregation in room temperature ionic liquids. *Journal of Physical Chemistry B*, 111(18), 4641–4644. <https://doi.org/10.1021/jp067705t>
- Uekama, K., Hirayama, F., & Irie, T. (1998). Cyclodextrin Drug Carrier Systems. *Chemical Reviews*, 98(5), 2045–2076.
- Valente, A. J.M., Carvalho, R. A., Murtinho, D., & Söderman, O. (2017). Molecular Dynamics of Cyclodextrins in Water Solutions from NMR Deuterium Relaxation: Implications for Cyclodextrin Aggregation. *Langmuir*, 33(33), 8233–8238. <https://doi.org/10.1021/acs.langmuir.7b01923>
- Valente, Artur J M, Carvalho, R. A., & Söderman, O. (2015). Do Cyclodextrins Aggregate in Water? Insights from NMR Experiments. *Langmuir*, 31(23), 6314–6320. <https://doi.org/10.1021/acs.langmuir.5b01493>
- Van Der Spoel, D., Lindahl, E., Hess, B., Groenhof, G., Mark, A. E., & Berendsen, H. J. C. (2005). GROMACS: Fast, flexible, and free. *Journal of Computational Chemistry*, 26(16), 1701–1718. <https://doi.org/10.1002/jcc.20291>
- Wang, H., Gurau, G., & Rogers, R. D. (2012). Ionic liquid processing of cellulose. *Chemical Society Reviews*, 41(4), 1519. <https://doi.org/10.1039/c2cs15311d>

- Weingärtner, H. (2008). Understanding Ionic Liquids at the Molecular Level: Facts, Problems, and Controversies. *Angewandte Chemie International Edition*, 47(4), 654–670. <https://doi.org/10.1002/anie.200604951>
- Welton, T. (1999). Room-temperature ionic liquids. Solvents for synthesis and catalysis. *CHEMICAL REVIEWS*, 99(8), 2071–2083.
- Youngs, T. G. A., Holbrey, J. D., Mullan, C. L., Norman, S. E., Lagunas, M. C., D'Agostino, C., Mantle, M. D., Gladden, L. F., Bowron, D. T., & Hardacre, C. (2011). Neutron diffraction, NMR and molecular dynamics study of glucose dissolved in the ionic liquid 1-ethyl-3-methylimidazolium acetate. *Chemical Science*, 2(8), 1594–1605. <https://doi.org/10.1039/c1sc00241d>
- Yu, Y., Li, J., Sun, Y., Liang, Q., Peng, X., Liu, Y., & Hu, Y. (2008). Solubility of β -cyclodextrin in different mixed solvents. *Petroleum Science*, 5(3), 263–268. <https://doi.org/10.1007/s12182-008-0044-y>
- Zhang, H., Ge, C., Van Der Spoel, D., Feng, W., & Tan, T. (2012). Insight into the structural deformations of beta-cyclodextrin caused by alcohol cosolvents and guest molecules. *Journal of Physical Chemistry B*, 116(12), 3880–3889. <https://doi.org/10.1021/jp300674d>
- Zheng, Y., Xuan, X., Wang, J., & Fan, M. (2010). The enhanced dissolution of β -cyclodextrin in some hydrophilic ionic liquids. *Journal of Physical Chemistry A*, 114(11), 3926–3931. <https://doi.org/10.1021/jp907333v>