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In this Issue:

Obituary:
Frank H. Field

Critical Insight:
Direct Inject ESI

Articles on:
- Proteins and Protein Biophysics
- Peptides
- High Resolving Power FTICR
- Ionization Developments
- MALDI
- Small Molecule Analysis
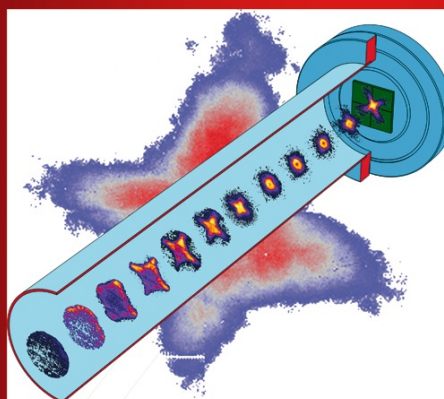
Active pixel detector for mass resolved images of a MALDI ion cloud, see page 809.

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RESEARCH ARTICLE

Inclusion Complexes of Ionic Liquids and Cyclodextrins: Are They Formed in the Gas Phase?

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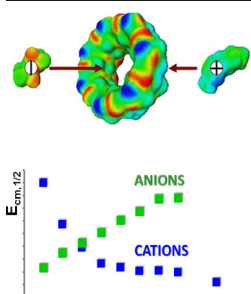
Abstract. The interaction of imidazolium-based ionic liquids with α- and β-cyclodextrins was investigated by electrospray ionization mass spectrometry with variable collision induced dissociation energy and quantum chemical gas-phase calculations. The center-of-mass energy at which 50 % of a precursor ion decomposes ($E_{cm,1/2}$) was determined for the isolated [cyclodextrin + cation]$^+$ or [cyclodextrin + anion]$^-$ adduct ions of imidazolium-based ionic liquids with different alkyl chain lengths combined with a large set of anions, such as chloride, bromide, bis(trifluoromethylsulfonyl)imide, tetrafluoroborate, hexafluorophosphate, trifluoromethanesulfonate, methanesulfonate, dicyanamide, and hydrogensulfate. Moreover, both symmetric and asymmetric imidazolium cationic cores were evaluated. The relative interaction energies in the adduct ions were interpreted in terms of the influence of cation/anion structures and their inherent properties, such as hydrophobicity and hydrogen bond accepting ability, in the complexation process with the cyclodextrins. The trends observed in the mass spectral data together with quantum-chemical calculations suggest that in the gas phase, cations and anions will preferentially interact with the lower or upper rim of the cyclodextrin, respectively, as opposed to what has been reported in condensed phase where the formation of an inclusion complex between ionic liquid and cyclodextrin is assumed.

Keywords: Ionic liquids, Cyclodextrin, Inclusion, Electrospray-ionization, Collision-induced-dissociation, Electronic-structure calculations

Introduction

Cyclodextrins (CD) are a group of cyclic oligosaccharides composed of α(1,4)-linked glucopyranose units. The three major cyclodextrins (α-, β-, and γ-cyclodextrins) comprise six, seven, and eight units, having a torus-like shape of 7.9 Å height and a cavity diameter ranging from 4.7 to 5.3 Å for α-CD, 6.0 to 6.5 Å for β-CD and 7.5 to 8.3 for γ-CD [1]. The formation of a host-guest complex between these (or other) macrocycles and diverse chemical species [2, 3] is an important feature in molecular recognition, drug delivery, and molecular machines [4].

Ionic liquids (ILs) [5–7] are defined as salts composed solely of ions, with a melting point below 100 °C and which have attracted a great deal of interest because of their wide liquidus range, low volatility, non-flammability, high thermal stability, and the possibility of fine-tuning their physical, chemical, and biological properties by an appropriate combination of the cationic and anionic chemical structures. An emerging field of IL application suggests its use as active pharmaceutical ingredient [8] in a pure liquid salt form that would overcome recurrent problems, such as polymorphism, limited solubility, bioavailability, and delivery capability found in the traditional crystalline forms.

The inclusion of ILs into cyclodextrins (CD) has been the subject of several recent publications, which have focused on stoichiometries and structures of inclusion complexes, binding constants, and thermodynamic parameters of complexation. Gao et al. used powder X-Ray diffraction and NMR spectroscopy to describe the formation of 1:1 and 1:2 complexes between β-cyclodextrin and 1-alkyl-3-methylimidazolium hexafluorophosphate ILs, [$C_nC_1$im][PF_6] (n = 12, 14, and 16) [9] and 1:1 complex for n = 4 [10]. François et al. [11] calculated the complexation constants of several imidazolium-based ILs combined with the anions bis(trifluoromethylsulfonyl)imide ([NTf_2]$^-$), [BF_4]$^-$, and Br$^-$, and α-, β-, and γ-cyclodextrins,

derived from affinity capillary electrophoresis data. Conductimetry and microcalorimetry results also provided the association constants for vinylimidazolium-[NTf$_2$]-based salts with β-cyclodextrin and its influence on polymerization [12, 13]. He at al. [14, 15] provided a detailed study of the interaction of [C$_4$C$_1$im][NTf$_2$], [C$_6$C$_1$im]Cl, and [C$_{12}$C$_1$im][NTf$_2$] with β-cyclodextrin using a competitive fluorescence method, conductivity, and ^{19}F NMR spectroscopy data. Moreover, combining these data with literature results, the authors established a sequence of interaction strength between ILs and β-CD based on the values of their association constants. An association pattern where simultaneous interaction of both the cation and anion with β-CD occurs via a two-step mechanism was also proposed by the authors [15]. Recently, Ondo et al. [16] addressed the problem previously noted by Zhang et al. [17] that the measured association constants of, for example, [C$_n$C$_1$im][PF$_6$]-β-CD, represent the weighing average of the association constants of the pairs [C$_n$C$_1$im]$^+$-β-CD, [PF$_6$]$^-$-β-CD, and [C$_n$C$_1$im][PF$_6$]-β-CD, and published a study where isothermal titration microcalorimetry measurements were performed not directly on ILs but on salts containing just the hydrophobic IL ion moiety and a complexation inactive counter ion. However, a large disagreement has been found in the open literature concerning the complexes structures in terms of which ion moiety or part of ion moiety fits inside the cyclodextrin cavity. A recent NMR and isothermal titration calorimetry study by Rak et al. [18] claims to have solved this issue by postulating that in the case of [C$_4$C$_1$im][PF$_6$], it is the anion and not the cation that forms a weak inclusion complex with β-cyclodextrin. Inclusion of dicationic ILs with β-cyclodextrins has also been addressed [19, 20]. The relevance of the ILs–cyclodextrins interactions has been demonstrated in extraction and chromatographic methods where ILs are used as solvents and also in the changes induced in physicochemical properties of both ILs and cyclodextrins [9, 21, 22].

The use of mass spectrometry in the field of supramolecular chemistry has attracted much attention because of the possibility of transferring noncovalent complexes from solution to the gas phase using electrospray ionization [23–26]. However, the gas phase results should be analyzed with care, mainly because of the possibility of the occurrence of unspecific binding instead of formation of an inclusion complex and because of changes in the relative importance of the several driving forces for the formation of the complex during the transition from solution to gas phase [27–31].

Here we report the ESI-MS-MS study with variable collision induced dissociation of the complexes of α- and β-cyclodextrins with imidazolium-based ionic liquids complemented with quantum chemical gas-phase calculations. The influence of the anion structure and cation alkyl side chain length on the relative interaction strength between the cyclodextrins and the isolated ions, measured as the dissociation energies E$_{cm,1/2}$ of the adduct ions, will be discussed in terms of the dominant interaction forces in the gas phase, compared with available solution data. Furthermore, agreement between the mass spectrometric experimental data and the total electronic energy changes during adduct formation will be assessed.

Experimental and Computational Details

Materials

The ionic liquids studied are listed in Table 1 and were purchased from IoLiTec (Freiburg, Germany) or Solchemar (Lisboa, Portugal). All ionic liquid samples presented mass fraction purities >99 %. α-, β- and γ-Cyclodextrins, were used without further purification. For the ESI-MS and ESI-MS-MS experiments, equimolar mixtures of cyclodextrin and ionic liquids, in HPLC grade methanol, at concentrations of ~10^{-4} mol · dm^{-3} were used.

Mass Spectrometry

Electrospray ionization mass spectra (ESI-MS) and tandem mass spectra (ESI-MS-MS) were acquired with a Micromass Q-Tof 2 (Micromass, Manchester, UK), operating in the positive (or negative) ion mode, equipped with a Z-spray source. Source and desolvation temperatures were 353 and 423 K, respectively. Ionic liquid and cyclodextrin mixtures in methanol were introduced at a 10 μL · min^{-1} flow rate. The capillary voltages were 3,000 V (for positive mode) and 2,600 V for the negative mode. The cone voltage was 30 V. Nitrogen was used as nebulization gas and argon as collision gas.

ESI-MS-MS spectra were acquired by selecting the precursor ion (CD-ILcation or anion adduct) with the quadrupole, performing collisions with argon at variable energies (E$_{Lab}$) in the hexapole, and analyzing the fragment ions thus produced with the TOF analyzer. The spectra represent an average of approximately 100 scans and triplicate measurements performed for each selected precursor ion. The standard deviations obtained varied between 0.3 % and 5 %. To implement energy-variable collision induced dissociation, the applied collisional activation voltage (E$_{Lab}$) is increased by small increments while the relative abundances of the precursor and fragment ions are monitored. The energy required to dissociate 50 % of the precursor ion was registered as E$_{Lab,1/2}$. In this inelastic collision of the projectile ion with the neutral target, the total available energy for conversion of translational (or kinetic) to internal (or vibrational) energy of the projectile ion is the center of mass energy, which can be calculated from E$_{Lab,1/2}$ and the masses for the neutral target (m$_t$) and precursor ion (m$_p$)

$$E_{cm} = E_{Lab}\left(\frac{m_t}{m_p + m_t}\right) \quad (1)$$

The E$_{cm,1/2}$ values obtained for each [α-, β-, and γ-cyclodextrin + C$_n$C$_1$im]$^+$, and [β-cyclodextrin + C$_n$C$_n$im]$^+$

Table 1. Cations and Anions Combinations of the ILs Studied

Cations
$[C_nC_1im]^+$
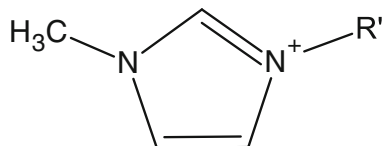
R' = $[C_nH_{2n+1}]$ (n=1-14)

$[C_nC_nim]^+$
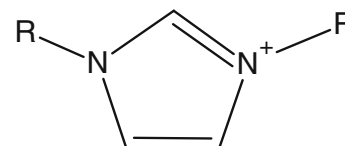
R = $[C_nH_{2n+1}]$ (n=1-12)

Anions

Chloride, Cl^-; bromide, Br^-; tetrafluoroborate, $[BF_4]^-$; hexafluorophosphate, $[PF_6]^-$; trifluoromethanesulfonate, $[CF_3SO_3]^-$; methanesulfonate, $[CH_3SO_3]^-$; dicyanamide, $[N(CN)_2]^-$; hydrogensulfate, $[HSO_4]^-$; bis(trifluoromethylsulfonyl)imide, $[NTf_2]^-$.

complexes were also corrected for the effect of the degrees of freedom on the rate constant of the complex dissociation, using the following Equation [32, 33]:

$$E_{cm,\frac{1}{2}}(corrected) = E_{cm,\frac{1}{2}}(complex) \cdot \frac{DOF_{reference}}{DOF_{complex}} \quad (2)$$

in which $DOF_{complex}$ refers to the degrees of freedom of the complex under study and $DOF_{reference}$ to the degrees of freedom of a reference complex, chosen to be the [α-cyclodextrin + C_1C_1im]$^+$.

Quantum Chemical Gas-Phase Calculations

In quantum chemical gas phase calculations, the ions $[NTf_2]^-$, $[BF_4]^-$, $[PF_6]^-$, Cl^-, and $[C_4mim]^+$, β-CD, and the β-CD-ion adduct geometries were optimized at the BP-TZVP level of theory, as well as with the B3LYP/6-31G(d)//HF/3-21G model chemistry, as implemented in Gaussian03 revD.02 [34]. In the literature, some information on DFT gas-phase structures of ß-CD is available [35]. The o(++) conformer was chosen; although it is not the energetically most stable conformer, its geometry is more close to the one experimentally observed in the crystal structure [36]. After independently optimizing the constituting ions, different initial guess conformations of the adducts were prepared, with the ionic species placed in proximity of the upper and lower rims, crossing the diameter of the torus in 1 Å-steps, as well as right inside the cavity (center and near the walls). Then, initial geometries were optimized; vibrational analysis to confirm the presence of true local minima on the potential energy surface could only be obtained for the B3LYP/6-31G(d)//HF/3-21G model chemistry. For the respective adducts, counterpoise corrections were applied [37, 38]. Mulliken population analysis, natural population analysis (NPA), and electrostatic potential-derived CHelpG charge calculations were conducted for β-CD at the B3LYP/6-31G(d) level of theory; coordinates and resulting Mulliken, NPA, and CHelpG charges, as well as electrostatic surface potentials for all atoms, are given as Supplementary Material

SM3. The differences in total electronic energies regarding [β-CD-ion]-adduct formation were calculated.

Results and Discussion

Electrospray ionization mass spectra (ESI-MS) of 1:1 mixtures of ionic liquid (IL) and cyclodextrin (CD) presented some common features. In the positive ion mode, peaks corresponding to [CD + H]$^+$, [CD + 2H]$^{2+}$, and [CD + ILcation]$^+$ ions were observed, whereas in the negative ion mode, [CD–H]$^-$, [CD–2H]$^{2-}$, and [CD + ILanion]$^-$ ions were recorded, showing the formation of a noncovalent adduct ion between the cyclodextrin and the cation or anion of the IL. The focus of the present study will be the analysis of the collision induced dissociation spectra (ESI-MS-MS) of the adduct ions [CD + ILcation]$^+$ and [CD + ILanion]$^-$, in which the only fragment ion observed is the cation (positive ion mode) or the anion (negative ion mode) (see Supplementary Material, SM1). From the collision energy necessary to dissociate 50 % of the precursor ion (CD + ILcation or anion), $E_{Lab,1/2}$, and using Equation 1, the respective values of the centre of mass energy, $E_{cm,1/2}$, were calculated. These calculated gas-phase dissociation energies (see Supplementary Material, SM2) represent the energy that is necessary to separate a cation (or anion) from the CD-ILcation or anion adduct in the gas phase and, as such, can be considered a good approximation to the IL–cation or anion–CD interaction strength in the absence of solvent. The analysis of these data involves the comparison of dissociation energies of α-, β-, and γ-cyclodextrins complexes with different sized cations $[C_nC_1im]^+$ (n = 1–10) and $[C_nC_nim]^+$ (n = 1–12), which will bring about an increase in the number of degrees of freedom of the dissociating ion. According to the simple RRK theory, the collision energies necessary to dissociate 50 % of larger precursor ions will be higher than expected solely on the basis of interaction strength within the complex because the redistribution of the internal energy amongst a higher number

of degrees of freedom will slow the fragmentation reaction [39, 40]. The compensation for this effect was achieved by correction of the measured $E_{cm,1/2}$ values for the complexes [α-, β-, γ-CD + ILcation]$^+$ relative to a selected reference ([α-CD + C_1C_1im]$^+$ complex) using the formula [32, 33] displayed in the experimental part, and assuming that all the other factors in the RRK expression for the rate constant are equal.

The formation of host–guest complexes in solution is believed to be a combination of several driving forces, namely, desolvation of the apolar host cavity and guest (hydrophobic effect), relief of conformational strain upon complexation, van der Waals interactions, and hydrogen bonding. Upon transfer of the complex from solution to gas phase, the hydrophobic effect due to the release of solvent molecules from the cavity to the bulk is absent, and the electrostatic interactions in a medium of lower dielectric constant will become significantly more important in the gas phase. The possibility of formation of unspecific adducts due to electrostatic interactions outside the cavity of the host, as opposed to inclusion inside the cavity, has always to be considered when analyzing mass spectrometry data.

Collision Induced Dissociation of [CD + ILanion]$^-$ Adducts

The $E_{cm,1/2}$ values for the complexes of α- and β-cyclodextrin with the anion of the [C_4C_1im][X] ionic liquid (X = [NTf$_2$]$^-$, [PF$_6$]$^-$, [CF$_3$SO$_3$]$^-$, [BF$_4$]$^-$, [N(CN)$_2$]$^-$, [HSO$_4$]$^-$, [CH$_3$SO$_3$]$^-$, and Br$^-$) are shown in Figure 1. Concerning the concept of matching size between the guest and the cyclodextrin cavity, the differences between α- and β-CD, in terms of relative interaction strength, are not significant. Moreover, the comparison of data in Figure 1 with the equilibrium constants for the reaction

$$\text{Anion} + \beta\text{-CD} \rightleftharpoons [\text{anion} + \beta\text{-CD}]^- \qquad (3)$$

determined by isothermal titration calorimetry [16], K_{11}([NTf$_2$]$^-$) = 3340, K_{11}([PF$_6$]$^-$) = 120, K_{11}([CF$_3$SO$_3$]$^-$) = 57 and K_{11}([BF$_4$]$^-$) = 31, shows that the gas phase data follow a reverse trend compared with solution phase data. The binding affinities between IL anions and cyclodextrins determined by the authors were mainly rationalized in terms of hydrophobic interactions and guest–host size matching, although the authors did not exclude the contribution of hydrogen bonding for the stability of the complexes [16]. As expected, no direct correlation between the $E_{cm,1/2}$ values and the hydrophobicity of anions, measured as log P(o/w) [41], was observed for the gas-phase complexes of α- and β-CDs with the IL anions, as shown in Figure 2. On the contrary, the plot of hydrogen bond accepting ability (parameter β) [42], formerly introduced by Kamlet and Taft for organic solvents, with the relative interaction strength between the anion and the cyclodextrins, demonstrates that the increase in basicity of the anion is accompanied by an increase in the interaction within the complex. This gas-phase behavior is interpreted as an indication of the preponderance of hydrogen bond formation between the anions and the hydroxyl groups at the rim of the cyclodextrins, the anion being probably located in the hydrophilic plane defined by the primary hydroxyl groups, as supported by the quantum chemical calculations discussed below. Previous solution studies focused on the investigation of the interaction between small anions and cyclodextrins [43–51] have also postulated this type of interaction.

Collision Induced Dissociation of [CD + ILcation]$^+$ Adducts

In the second part of this study, the influence of the alkyl side chain length of the imidazolium cation was analyzed through the determination of the $E_{cm,1/2}$ values for the complexes [α-or β-CD + $C_nC_1$im]$^+$ (n = 1–10) with bis(trifluoromethylsulfonyl)imide ([NTf$_2$]$^-$) as the fixed counter ion. First, an experiment designed to evaluate the influence of the cation–anion interaction within the ionic liquid in the
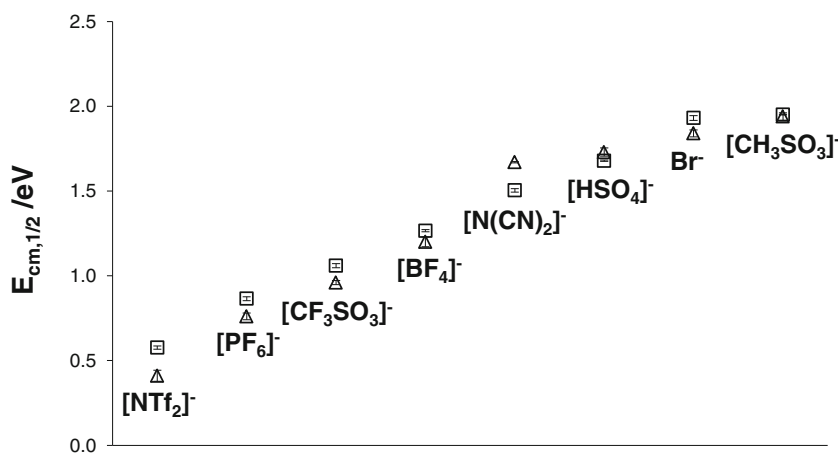

Figure 1. $E_{cm,1/2}$ dependence with the IL anion for the complexes [α-cyclodextrin + anion]$^-$ (△) and [β-cyclodextrin + anion]$^-$ (□)

interaction of cyclodextrin with the cation was performed, by measuring $E_{cm,1/2}$ values for the complexes $[\beta\text{-CD} + C_4C_1im]^+$ with the following counter ions: chloride, methanesulfonate, dicyanamide, and bis(trifluoromethylsulfonyl)imide. The differences between the $E_{cm,1/2}$ values are not statistically significant (Supplementary Information SM5). The interpretation of the gas-phase results will require a previous discussion of condensed phase complexation of ionic liquids with cyclodextrins. In solution, a general interaction pattern [15] was proposed, which consists of the following: the ILcation or the anion first interacts with β-cyclodextrin, and 1:1 (IL:CD) complexes are formed. If both the cation and the anion of an IL interact strongly with cyclodextrin, 1:2 (IL:CD) complexes will be formed, which can dissociate into cation-β-CD and anion-β-CD. The multiple interactions (anion–cation, cation–CD, and anion–CD) that occur in an aqueous solution of IL and CD, besides the hydrogen bonding with water, will determine the stoichiometry of the complexes formed, and most likely the relative orientation of the cation inside the cyclodextrin cavity. Besides the interaction of the anion from the IL-ion pair with the rim or the outside of the CD cavity, will probably contribute to the complex conformation. According to the gas phase results presented above, which show no influence of the anion on the $E_{cm,1/2}$ values for the complex $[\beta\text{-CD} + C_4C_1im]^+$, solution-phase conformations are not preserved in the ESI transfer from solution to gas phase. This issue, which has always been a matter of debate [52], was addressed in a recent study on the role of water in the interaction of α,ω-alkyldiammonium ions with cucurbit[n]urils [53]. Based on solution, gas-phase, quantum chemical calculations, and molecular dynamics,

the authors postulated that the gas-phase conformational change of the alkyl chain of the guest inside the host cavity, in order to maximize ion–dipole interactions, is absent in the presence of water. This is expressed by the differences between solution and gas-phase stabilities of the complexes.

The increase of the alkyl chain length in the imidazolium cation causes initially a marked decrease on the interaction strength between α- or β-cyclodextrin and the $[C_nC_1im]^+$ cation from $n = 1$ to $n = 4–5$, followed by a tendency almost independent of a further increase in the number of carbon atoms (Figure 3). Also noteworthy in these data are the much lower energy values for the dissociation of the $[CD + cation]^+$ adducts (0.39–0.59 eV) than for the anions (0.41–1.94 eV; Figure 1), in agreement with previous theoretical and solution studies [43, 46]. Condensed phase data for the interaction of imidazolium-based ionic liquids with cyclodextrins show an increase of the association constant with the increase of the alkyl chain length, interpreted as a consequence of hydrophobic and van der Waals interactions due to the inclusion of the alkyl chain inside the cyclodextrin cavity [9–11, 15–17]. Available literature data on alkylamines [54, 55], α,ω-dicarboxylic [56] acids, and alkyl trimethylammonium bromides [57] with cyclodextrins show similar trends in aqueous solution. A comparison between the gas-phase behavior of linear alkylammonium and methylimidazolium complexes was carried out by measuring the $E_{cm,1/2}$ values for ethylammonium, butylammonium, and pentylammonium complexes with β-cyclodextrin. The results show that for linear alkylammoniums ions, there is an increase in interaction strength from ethylammonium to pentylammonium complexes, whereas for the corresponding 1-alkyl-methyl-imidazolium complexes the trend is reversed. These results point to inclusion of the aliphatic chain of alkylammonium ions inside the cavity of the macrocycle, whereas for 1-alkyl-methyl-imidazolium complexes the linear hydrocarbon part of the ion would remain outside. The important role played by the imidazolium cation in the complexation process that occurs in the gas phase seems evident from these results. Assuming that the formation of the adducts $[CD + ILcation]^+$ is mainly driven by the interaction of the imidazolium ring with the outer rim of the cyclodextrin, the alkyl chain pending outside, we decided to extend the study to symmetric 1,3-dialkylimidazolium-based ionic liquids of the general formula $[C_nC_nim][NTf_2]$. Although the dissociation energies for both cations follow the same general trend with the increase in the number of carbon atoms, there is a more pronounced decrease in energy from $n = 2$ to $n = 3$ within the symmetrical cation adducts (Figure 4). This might be explained as a consequence of steric hindrance to the approach of the imidazolium cation to the cyclodextrin caused by the existence of the two alkyl chains. The gas-phase results just presented can be interpreted assuming that the longer alkyl chain will remain outside the cavity of the cyclodextrin and the interaction within the adduct will predominantly take
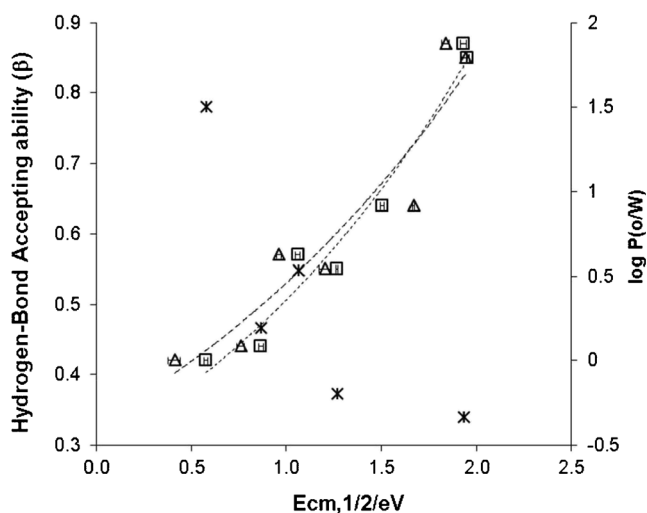

Figure 2. $E_{cm,1/2}$ (corrected) dependence with the hydrogen-bond accepting ability (□) [37] of the anions $[NTf_2]^-$, $[PF_6]^-$, $[CF_3SO_3]^-$, $[BF_4]^-$, and Br^- for the complexes [α-cyclodextrin + anion]$^-$ (△) and [β-cyclodextrin + anion]$^-$ (□), and with hydrophobicity expressed as log P(o/w) [41] for the complex [β-cyclodextrin + anion]$^-$ (*)
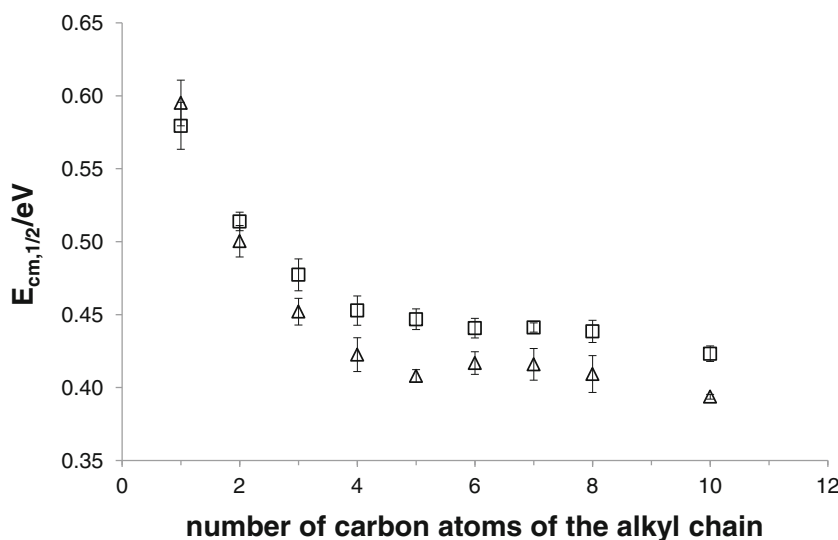
Figure 3. $E_{cm,1/2}$ (corrected) dependence with the number of the carbon atoms (n) of the alkyl chain for the complexes [α-cyclodextrin + $C_nC_1$im]$^+$ (△) and [β-cyclodextrin + $C_nC_1$im]$^+$ (▢)

place through the imidazolium ring. Increasing the cyclodextrin cavity size has the effect of slightly increasing the value of $E_{cm,1/2}$, from α- to β-cyclodextrin (Figure 3) and of decreasing from β- to γ-cyclodextrin ($E_{cm,1/2}$ (corrected) = 0.355 eV for the [γ-CD + C_4C_1im] + ion), the latter being explained by a greater distance between the rim and the cation, which loosens the interaction strength [3].

Quantum Chemical Gas-Phase Calculations

In the course of geometry optimization at the BP-TZVP level of theory of the CD-ion adducts (Supplementary Material, SM4), the CD cavity showed a tendency of staying nearly clear of ions, which where consecutively forced out, away from the inner center of the cavity, and finally settling in close proximity to the rims. Due to the adduct size, frequency calculations could not be performed at this level of theory.

In accordance with the interpretation given above on possible hydrogen bond formation, minimum structures of CD-anion adducts show an anionic preference of the partial positive areas at the upper rim, whereas the $[C_4C_1$im]$^+$ cation will suit itself in the outer proximity of the lower rim, with the imidazolium moiety faced nearly perpendicular at the lower cavity entrance, with the
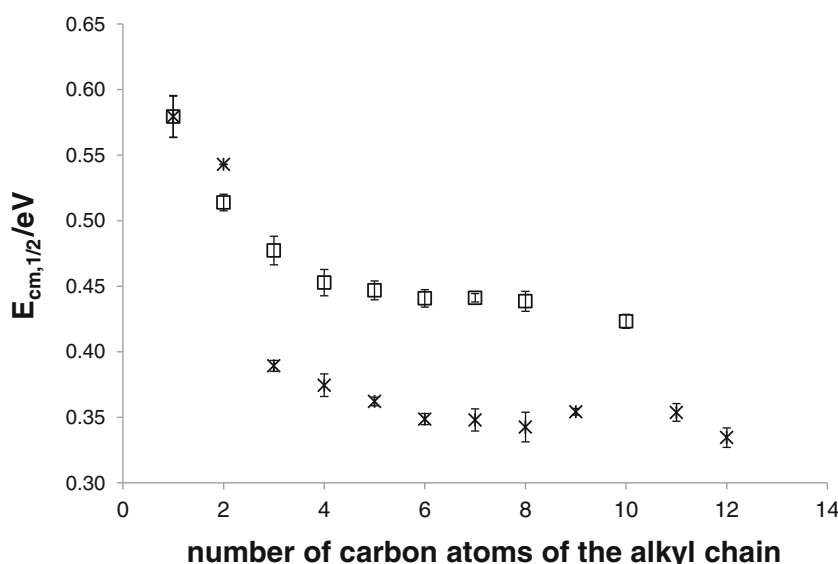

Figure 4. $E_{cm,1/2}$ (corrected) dependence with the number of carbon atoms (n) of the alkyl chain for the complexes [β-cyclodextrin + $C_nC_1$im]$^+$with asymmetric alkylimidazolioum cations (▢) and symmetric dialkylimidazolium cations, [β-cyclodextrin + $C_nC_n$im]$^+$
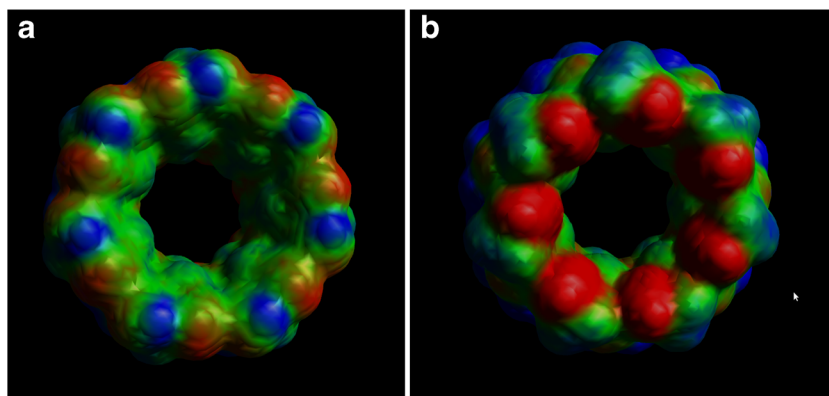
Figure 5. Electrostatic surface potential plot of β-CD as obtained at the B3LYP/6-31G(d) level of theory; **(a)** top view, **(b)** bottom view

methyl group entering the cavity. These preferential ionic settling areas in adduct formation become more comprehensible when inspecting the electrostatic surface potential of β-CD, as derived from quantum chemical gas-phase calculation at the B3LYP/6-31G(d) level of theory and depicted in Figure 5 (more details on the atomic charges are given as Supplementary Material, SM3). Here, alternating charge distributions between local concentrations of positive and negative charges of the upper rim contrast with prevailing negatively charged oxygen vicinities on the lower rim, while the inner cavity stays mainly non-polar.

To obtain an idea about the energetic magnitude of adduct formation of β-CD-anion adducts, total electronic energies of all species (β-CD, anions, and [anion + β-CD]$^-$-adducts) were taken from calculations at the B3LYP/6-31G(d)//HF/3-21G model chemistry, and the respective changes during adduct formation were calculated. Adduct formation of β-CD with anions of high symmetry and delocalized charge over four ([BF$_4$]$^-$) or six ([PF$_6$]$^-$) donor atoms, or with an anion featuring delocalization of the negative charge by conjugation over several atoms ([NTf$_2$]$^-$), are accompanied by an energetic effect of similar magnitude, whereas an adduct formation with Cl$^-$ is significantly more exothermic, as is shown in Table 2. The qualitative trend of total electronic energy changes during adduct formation supports our finding derived above from collision induced dissociation results of [anion + β-CD]$^-$-

Table 2. Calculated Total Electronic Energy Changes During [Anion + β-CD]$^-$ Adduct Formation ($\Delta_R\varepsilon_{add}$), Corresponding to Equation 3, as Obtained from the B3LYP/6-31G(d)//HF/3-21G Model Chemistry

Anion + β-CD → [anion + β-CD]$^-$	$-\Delta_R\varepsilon_{add}$/(kJ.mol^{-1})
NTf$_2^-$ + β-CD → [NTf$_2$ + β-CD]$^-$	30.0
[PF$_6$]$^-$ + β-CD → [PF$_6$ + β-CD]$^-$	41.4
[BF$_4$]$^-$ + β-CD → [BF$_4$ + β-CD]$^-$	55.5
Cl$^-$ + β-CD → [Cl + β-CD]$^-$	153.0

adducts: that the experimental gas phase data follow a reverse trend compared with data obtained in solution phase.

Solution vs. Gas-Phase Complexation

Molecular dynamics simulations suggest a strong stabilization effect accompanying the formation of ionic inclusion complexes of CD in the gas phase, with electrostatic interactions as the main source. This association is combined with strong reorganizations of the CD basket skeleton with the ionic groups appearing outside [58]. In contrast, in solvents of high polarity such as water, additional large amounts of ion-specific desolvation energies are needed for the binding of an ionic guest, suppressing its binding affinity and resulting, to a varying degree, in enthalpy-entropy compensation of the CD adduct formation. Although in the gas phase all adducts are expected to have unfavorable entropies because of the loss of translational degrees of freedom, a similar statement for the solution phase cannot be as straightforward because of the above-mentioned interplay of various factors. Enthalpies of adduct formation are exothermic in gas phase and solution phase, but both their absolute values do not follow an equal trend. In solution experiments on complexation of ionic species with cyclodextrins, it was elucidated that larger anions interact more strongly with CD than do smaller anions. This was partially attributed to the relative ease of desolvation of the larger anion [59]. Although adduct formation in solution is more exothermic for anions featuring charge delocalization or conjugation [16], the reverse seems to be true for the gas phase, where electrostatic interactions with smaller anions result in the more exothermic adduct formation reactions. The analysis and interpretation of the collision induced dissociations of the adducts of cyclodextrin and ILs anions and cations presented in previous sections, together with comparison of available solution data, provide an experimental illustration of the

differences between gas phase and solution chemistry in these complexes.

Conclusions

A systematic study of the interactions between α- and β-cyclodextrins with 1-alkyl-3-methylimidazolium-based ILs, $[C_nC_1im]^+$ (n = 1–14), combined with the anions chloride, bromide, tetrafluoroborate, hexafluorophosphate, trifluoromethanesulfonate, methanesulfonate, dicyanamide, hydrogensulfate, and bis(trifluoromethylsulfonyl)imide was carried out using electrospray ionization mass spectrometry with variable collision induced dissociation energy and quantum chemical gas-phase calculations. Moreover, 1,3-dialkylimidazolium bis(trifluoromethylsulfonyl)imide ILs were also addressed to ascertain on the cation symmetry effect. The main conclusions drawn from the combined analysis of data are the following: (1) The $E_{cm,1/2}$ values for the cyclodextrins-anions interactions follow the trend observed for the known hydrogen bond accepting ability of the anions and not that of the hydrophobicity, which shows that the main force responsible for the interaction is not the hydrophobic effect but the hydrogen bond formation between cyclodextrin and the IL anion. A good correlation among the calculated values for the total electronic energy changes during [anion + β-CD]⁻ adduct formation (anion = $[NTf_2]^-$, $[BF_4]^-$, and $[PF_6]^-$) and the experimental $E_{cm,1/2}$ was also found. (2) The $E_{cm,1/2}$ values for the cyclodextrin–cation interactions, either for $[C_nC_1im]^+$ or $[C_nC_nim]^+$, decrease significantly from $n = 1$ to $n = 4$–5, followed by a tendency to become independent of the increase in the number of carbon atoms in the alkyl chain. This behavior, which is the reverse of the reported condensed data, suggests that the alkyl chain is not located inside the cavity of the cyclodextrin because in the gas-phase, the imidazolium ring will preferentially interact with the rim of the cyclodextrin. Minimum structures optimization shows that the cation will suit itself in the outer proximity of the lower rim, with the imidazolium moiety faced nearly perpendicular at the lower cavity entrance, with the methyl group entering the cavity, in accordance to the mass spectral data conclusions; increasing the cyclodextrin cavity size has the effect of increasing slightly the value of $E_{cm,1/2}$ from α- to β-cyclodextrin and of decreasing from β- to γ-cyclodextrin, the latter being explained by a greater distance between the rim and the cation, which loosens the interaction strength.

As a general conclusion, the gas-phase experimental and theoretical data show clearly that neither the cation nor the anion form inclusion complexes with α- and β-cyclodextrins.

Acknowledgments

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