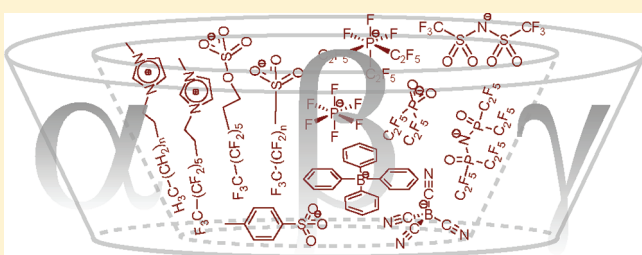


Interaction of Ionic Liquids Ions with Natural Cyclodextrins

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ABSTRACT: The interaction of natural α -, β -, and γ -cyclodextrins (CDs) with 14 hydrophobic ionic moieties of ionic liquids (ILs) was systematically examined in dilute aqueous solutions using isothermal titration microcalorimetry (ITC) and NMR spectroscopy. The studied cationic and anionic moieties involved some recently developed heavily fluorinated structures, as well as some others of common use. To isolate the effect of a given ion, the measurements were performed on salts containing the hydrophobic IL ion in question and a complexation-inactive counterion. Additional ITC experiments on ILs whose both cation and anion can interact appreciably with the CD cavity demonstrated that to resolve the effect of individual ions from such data is generally a tricky task and confirmed the superiority of the isolation strategy adopted for the purpose throughout this work. The binding constant, enthalpy and entropy determined at 298.15 K for the 1:1 (ion:CD) inclusion complex formation range in broad limits, being $0 < K < 2 \times 10^5$, $0 < -\Delta_r H^\circ / (\text{kJ} \cdot \text{mol}^{-1}) < 44$, and $-28 < T\Delta_r S^\circ / (\text{kJ} \cdot \text{mol}^{-1}) < 14$, respectively. The stabilities of complexes of perfluorohexyl bearing ions with β -CD belong to the highest ever observed with natural CDs in water. The established binding affinity scales were discussed in both thermodynamic and molecular terms. The concepts of hydrophobic interaction and guest–host size matching supported by simple molecular modeling proved useful to rationalize the observed widely different binding affinities and suggest possible binding modes. Enthalpy and entropy contributions to the stability of the ion-CD complexes were found to compensate each other considerably obeying more or less the linear compensation relationship marked by existing literature data on binding other guests to natural CDs. As outliers to this pattern, the most stable complexes of $-\text{C}_6\text{F}_{13}$ bearing ions with β -CD were found to receive an enhanced inherent entropy stabilization due to extraordinarily high extent of desolvation occurring in the course of binding.



1. INTRODUCTION

During the past decade, ionic liquids (ILs) have attracted considerable attention of the academic and industrial chemical community, because the unique physicochemical properties and environmentally friendly character of these substances offer a great variety of prospective applications. These molten salts with melting temperatures below 100 °C have been recognized as novel “designer” materials whose properties can be fine-tuned for specific tasks through the variation of the cation and anion structures.^{1,2} Stemming from the potential of an almost unlimited number of such variations, still new ILs are being prepared to extend the existing portfolio. For example, beside the traditional and widely examined BF_4^- , PF_6^- , and Tf_2N^- based ILs, some more sophisticated and hydrophobic ILs bearing the substituted tetraphenylborates,^{3,4} orthoborates,⁵ (metalla)carboranes,^{6,7} cyanoborates,⁸ tris(pentafluoroethyl)trifluorophosphate,⁹ and bis[bis(pentafluoroethyl)phosphinyl]imide¹⁰ anions have been synthesized in laboratories and even introduced to the market. Another interesting class of ionic liquids can be based on the polyfluoroalkylated imidazolium or sulfate ions recently presented by Kvíčala and co-workers.^{11–13}

In many applications of ILs, their interaction with other system components plays the decisive role and hence much of the current research on ILs deals with this issue. Among possible interaction partners of ILs, cyclodextrins (CDs) are of special interest since on IL-CD interaction new developments in separation, pharmaceutical, and polymer sciences could be based.^{14–16} Cyclodextrins are macrocyclic oligosaccharides known for the ability to encapsulate in their molecular cavity guest molecules of appropriate dimensions. Interactions of various substances with CDs have been extensively studied over several past decades, and thus quite good knowledge of the subject is currently available.^{17,18} However, as concerns specifically ionic liquids, respective information is, due to the relative novelty of these materials, still very limited.

The first qualitative study on the IL-CD complexation, namely of 1-butyl-3-methylimidazolium hexafluorophosphate ($[\text{C}_4\text{C}_1\text{Im}][\text{PF}_6]$) with β -CD in water, was presented by Gao

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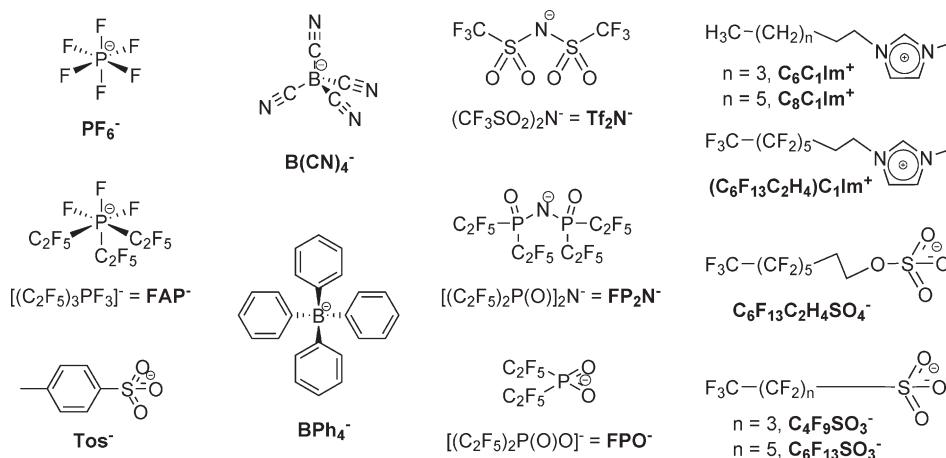
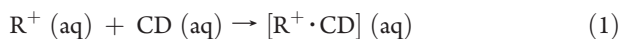


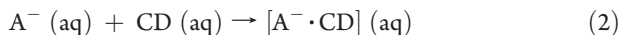
Figure 1. Molecular structures of the IL ions studied and their abbreviations used in this work.

et al.¹⁹ only in 2005. Using solubility and conductivity measurements, these authors indicated the formation of a 1:1 complex which they isolated in solid state and proved its structure by powder X-ray diffraction and ¹³C CP/MAS NMR spectroscopy. Since then, several qualitative and quantitative studies on the interaction of ILs with natural CDs in aqueous media appeared in the literature.^{20–26} Gao et al.^{20,21} studied qualitatively the interaction of β -CD with surface active ILs $[\text{C}_{12-16}\text{C}_1\text{Im}][\text{PF}_6]$. Using capillary electrophoresis, Francois et al.²² quantified the association of alkylimidazolium cations with a series of different natural and modified CDs. Amajjahe and Ritter²³ performed calorimetric measurements on the interaction of 1-butyl-3-vinylimidazolium bis[(trifluoromethyl)sulfonyl]imide ($[\text{C}_4\text{VIm}][\text{Tf}_2\text{N}]$) with natural α -, β -, γ -CDs, and randomly methylated β -CD. The most addressed and discussed topics were the complexation of $[\text{C}_4\text{C}_1\text{Im}]\text{Cl}$, $[\text{C}_4\text{C}_1\text{Im}][\text{BF}_4]$, and $[\text{C}_4\text{C}_1\text{Im}][\text{PF}_6]$ ILs with natural β -CD^{19,22,24} and the search for a plausible complexation mechanism and the structure of complexes.²⁵ In our recent contribution,²⁶ combining various NMR spectroscopy approaches and isothermal titration calorimetry (ITC) measurements, we have completely resolved the issue of binding $[\text{C}_4\text{C}_1\text{Im}][\text{PF}_6]$ with β -CD: the PF_6^- anion was identified to be unambiguously the guest entering the β -CD cavity and residing close to its narrow rim and the binding was found to be relatively weak ($K \approx 10^2$) and enthalpy driven.

In dilute aqueous solutions where the CD complexation studies are performed, ILs appear to be completely dissociated to ions.^{27,28} Thus, ILs (R^+A^-) can offer either cation



or anion



or both of their ionic moieties for the inclusion complexation with CDs. The question of which IL moiety (whether cationic or anionic or both) enters the CD cavity is very important for the understanding of inclusion phenomena and for their subsequent applications, but answering this question need not be easy. To overcome this problem and isolate the contributions of cation and anion, special experimental strategies or ion-/structure-specific experimental techniques can be used.

In this work, we conducted a systematic investigation of the interaction between hydrophobic IL ions and natural α -, β -, and γ -CDs in water. To this end, we performed extensive measurements by isothermal titration microcalorimetry (ITC) providing a complete thermodynamic characterization of respective inclusion complex formation. The use of the very sensitive technique of ITC allowed us to confirm the stoichiometry of the complex formed and simultaneously determine the binding constant, the enthalpy, and the entropy of complex formation from experiments at a single temperature only.

The molecular structures and denotations of the ions studied are depicted in Figure 1. All of the 14 ions selected for the study are hydrophobic in nature, in accordance with the fact that the hydrophobic interaction is typically the major driving force of the CD inclusion complexation. Note that most of the selected ions are rather heavily fluorinated, which is a feature also considered to promote the binding. The selection is focused on new IL ions for which the information on their interaction with CDs is totally missing. Nevertheless, some traditional IL ions (e.g., PF_6^- , Tf_2N^- , Tos^-) are also included, since the literature information on their interaction with natural CDs is incomplete (typically only the binding constant at 298.15 K is available) or inaccurate.

To isolate the effect of a given ion, the measurements were performed not directly on ILs but on salts containing just the hydrophobic IL ion moiety in question and a complexation-inactive counterion. As such counterions we selected small inorganic ions (Li^+ , Na^+ , K^+ , Cl^- , I^-) known to interact very weakly with the natural CDs^{29–31} so that their contribution to the observed complexation was negligible. This isolation method not only unambiguously identified the effect of an individual ion, but brought an additional convenience in higher solubilities, higher available purities, and lower costs of the salts compared to their respective ILs.

Although ITC is generally considered as an efficient probe of complex formation, it fails in special cases where the enthalpy effect upon complexation is small, i.e., for systems in which the complexation is fully entropy-driven. Thus, when in contrast with anticipation our ITC measurement did not indicate the complex formation, we additionally probed the interaction with NMR spectroscopy to avoid misinterpretation of the ITC result. The present methodical study of ILs ions binding to natural cyclodextrins enabled us to establish respective binding affinity scales and discuss them in both thermodynamic and molecular terms.

In order to rationalize the observed widely different binding affinities and suggest possible binding modes, we employed the concepts of hydrophobic interaction and guest–host size matching backed by simple molecular modeling.

Apart from the targeted investigations of the binding of IL ions and natural cyclodextrins using the isolation strategy, we also examined the interaction of the α -, and β -CDs with two selected $[C_nC_1Im][PF_6]$ ($n = 6, 8$) ILs in which both cation and anion are expected to bind appreciably to the CDs. We tested whether the ITC data obtained can be meaningfully analyzed to resolve the effects of the two complexation-active ions.

2. EXPERIMENTAL PART

2.1. Materials. The following salts were commercial samples used as received without further purification: lithium bis-[(trifluoromethyl)sulfonyl]imide ($Li[TF_2N]$, IoLiTec, Germany, 99.9%), sodium tetraphenylborate ($Na[BPh_4]$, Sigma-Aldrich, $\geq 99.5\%$), sodium toluene-4-sulfonate ($Na[Tos]$, Merck, 98%) potassium nonafluoro-1-butanefluorophosphate ($K[C_4F_9SO_3]$, Merck, 98%), and potassium tridecafluoro-1-hexanesulfonate ($K[C_6F_{13}SO_3]$, Sigma-Aldrich, 98%).

The following potassium salts were synthesized according to the patents and literature at Merck KGaA (Darmstadt, Germany): tetracyanoborate ($K[B(CN)_4]$),^{8,32} bis(pentafluoroethyl) phosphinate ($K[FPO]$),³³ tris(pentafluoroethyl)trifluorophosphate ($K[FAP]$),^{9,34} and bis[bis(pentafluoroethyl)phosphinyl]imide ($K[FP_2N]$).^{35,36}

1-[2-(Perfluorohexyl)ethyl]-3-methylimidazolium iodide ($[(C_6F_{13}C_2H_4)C_1Im]I$, water content 4.85% w/w)^{12,37} and potassium 2-(perfluorohexyl)ethyl sulfate ($K[C_6F_{13}C_2H_4SO_4]$, water content 13.1% w/w by Karl Fischer titration)¹³ were synthesized at ICT Prague according to the cited procedures, the 1H , ^{13}C , and ^{19}F NMR spectra of the obtained samples conforming perfectly with those reported previously.^{13,37}

The ionic liquids: 1-methyl-3-octylimidazolium chloride ($[C_8C_1Im]Cl$, 98%), 1-hexyl-3-methylimidazolium hexafluorophosphate ($[C_6C_1Im][PF_6]$, 99.5%), 1-methyl-3-octylimidazolium hexafluorophosphate ($[C_8C_1Im][PF_6]$, 99%) were purchased from Solvent Innovation (Germany), 1-hexyl-3-methylimidazolium chloride ($[C_6C_1Im]Cl$, 99.1%) from IoLiTec (Germany). Water content of the ILs studied was determined by Karl Fischer titration and was in all cases below 0.5% w/w.

The natural cyclodextrins were purchased from CycloLab (Hungary): α -cyclodextrin (α -CD, water content 11.0% w/w by Karl Fischer titration), β -cyclodextrin (β -CD, water content 13.9% w/w), and γ -cyclodextrin (γ -CD, water content 9.46% w/w). Water contents in both the electrolyte and the CD samples were duly considered to determine the concentrations of prepared solutions. Water used in the ITC measurements as the solvent was distilled and subsequently treated by Milli-Q Water Purification System (Millipore, USA). Hygroscopic compounds were handled in a glovebox under dry Ar or N_2 atmosphere.

2.2. Isothermal Titration Calorimetry. The heats of complexation were measured at 298.15 K using two different ITC instruments: VP-ITC from MicroCal (Northampton, MA, USA) and TAM-ITC from Thermometric (TA-Instruments, former Thermometric, Järfälla, Sweden). The parameters of the titration process, namely the injected volume, total number of injections, filling of the cell/syringe and time interval between injections, were adjusted in each particular case with respect to electrolyte and CD solubilities, reaction kinetics, and further conditions, in

order to achieve the best measurement accuracy and the highest possible conversion of reactants at the end of titration. Solutions were prepared by weight. The measured heats of complexation were corrected for mere dilution of the titrand in water, the dilution heats being measured in the same manner as the heats of complexation except for the fact that in the dilution experiments the reaction cell was filled with neat water. The instruments were checked periodically by the chemical test reaction of $BaCl_2$ (aq) with 18-crown-6 (aq); in these tests, we always observed excellent agreement (1–3%) in K and $\Delta_r H^\circ$ values with the most reliable literature data of Briggner and Wadsö.³⁸

2.2.1. VP-ITC. The VP-ITC is an ultrasensitive power compensating ITC. The calorimeter is equipped with a cell of 1.452 cm³ reaction volume and the titrand is added by means of a 278 mm³ syringe. In the present experiments, the titrations usually consisted of 25–55 consecutive injections of 5–15 mm³, with a 5–8 min time delay between injections and stirring of the cell content at 568 rpm spin rate. The concentrations of aqueous CDs ranged from 0.3 to 10 mmol·dm^{−3}, those of the electrolytes from 0.3 to 100 mmol·dm^{−3}. Prior filling the syringe and the cell the solutions were duly degassed. A typical run lasted 3–5 h. The measured heat data were processed using the ITC data analysis program provided by MicroCal to obtain thermodynamic characteristics of binding. An example: the $K[FAP]$ solution was filled into the reaction cell and was titrated with the α -, β -, and γ -CD solutions from the syringe; the concentration of $K[FAP]$ solution was 0.30 mmol·dm^{−3}, whereas the concentration of α -CD corresponded to 9.6 mmol·dm^{−3}, and those of β -CD and γ -CD to approximately 3.0 mmol·dm^{−3}; titrations consisted of 40 consecutive injections: the first injection of 1 mm³ was followed by next 23 of 5 mm³, and after by 16 injections of 10 mm³ with a 5 min time delay between injections.

2.2.2. TAM-ITC. The Thermal Activity Monitor 2277 model unit is a heat-flow isothermal titration calorimeter (TAM-ITC) equipped with a 4.5 cm³ titration cell with a maximum allowed liquid loading of 3.8 cm³. In the present experiments, aqueous electrolyte solutions were titrated into CD solutions by means of a motor driven pump (Hamilton Microlab M) coupled with a 100 mm³ Hamilton syringe. The titration process consisted of 20 injections of 10 or 25 mm³ into the reaction ampule filled with approximately 2.7 cm³ of the CD aqueous solution. The cannula was immersed into the sample 60 min before starting the titrations, the content of the ampule being stirred by a turbine stirrer. In complexation experiments, the intervals between consecutive injections were 60 min (main + baseline section = 45 + 15 min) and those in dilution experiments 45 min (main + baseline section = 35 + 10 min). Such long time intervals were essential to provide a good thermal stabilization. A typical TAM-ITC run, involving predynamic and poststatic electrical calibrations, then lasted 20–24 h. The heat data were processed using the ITC data analysis DigiTam program provided by Thermometric. With this calorimeter, the complexation of the ionic liquids $[C_6C_1Im]Cl$ and $[C_8C_1Im]Cl$ and of the salt $Li[TF_2N]$ with β -CD were measured. In each experiment, the concentration of electrolyte solutions used corresponded to 30–100 mmol·dm^{−3}, which for $[C_6C_1Im]Cl$ and $[C_8C_1Im]Cl$ is far below their critical micelle concentration.^{39,40} The concentration of β -CD was approximately 3.0 mmol·dm^{−3}.

2.3. NMR Spectroscopy. NMR spectroscopy was used to investigate the interaction between IL ions and CDs in cases for which the ITC experiment failed to provide reliable results due to a low level of the calorimetric signal. In this case 1H or ^{19}F NMR

titrations were performed in order to determine the value of the binding constant.⁴¹ The NMR spectra were recorded on a Varian Mercury Plus 300 MHz spectrometer (¹H NMR at 300.075 MHz, ¹⁹F NMR at 282.404 MHz) at a temperature of (298 ± 1) K. D₂O was used as a solvent for all NMR measurements. For correct referencing of individual spectra, an external standard in capillary consisting of a mixture of TMS (for ¹H NMR measurements) with hexafluorobenzene (for ¹⁹F NMR measurements) in CDCl₃ was used. In NMR titrations the concentration of the observed compound was always kept constant and the other compound was added stepwise as a solution containing also the observed compound. The additions were weighted. The binding constants *K* were evaluated from the changes of chemical shifts by nonlinear fitting.

3. RESULTS

3.1. Thermodynamic Quantities for Ion-CD Binding. Following the isolation strategy, the measured titration data were processed using a 1:1 stoichiometry complexation model to obtain the thermodynamic characteristics of the ion-CD binding. The equilibrium constant for the corresponding reaction is

$$K = \frac{c_{[\text{ion} \cdot \text{CD}]}}{c_{\text{ion}} c_{\text{CD}}} c^{\text{st}} \quad (3)$$

where *c* is the molar concentration of the indicated species. The standard state used for the solute is the hypothetical ideal solution of unit molarity (*c*st = 1 mol · dm⁻³). The nonideality corrections are assumed to be negligible: at conditions examined the uncharged species (CD) is effectively at infinite dilution and the activity coefficients of the charged species which would appear in the numerator and the denominator of eq 3 should largely cancel at even moderate ionic strengths. The fits of the titration curves for a single complexation-active ion by the 1:1 binding model proved to be adequate, sufficiently accurate, and robust. This fact was generally reflected by small fitting deviations, absence of any significant bias, and reasonably small uncertainties of calculated parameters. Also, trials to apply models of more complicated stoichiometry failed to give any improvement of the fits and lead to statistically meaningless values of additional parameters. Thus, the use of the 1:1 complexation model for the binding of a single ion to the CD is fully justified. For illustration, Figure 2 shows calorimetric data and their fits with the 1:1 complexation model for titration of an aqueous K[FAP] solution with aqueous α-, β-, and γ-CD solutions.

For principal reasons, the sensitivity of the ITC technique reduces for reactions having small *K* values and/or small absolute Δ_r*H*^o values. Solubility bounds may put additional limitations on the size of the measurable signal which further enhances the uncertainties of the calculated thermodynamic quantities. In order to cope with this issue, two or more titrations at different initial concentrations of the reactants were typically performed in this work for reactions with *K* < 400 and their thermodynamic parameters were calculated by fitting all the titration curves simultaneously. This procedure greatly improved the *K* and Δ_r*H*^o estimation.

In some instances, the ITC indicated, in contrast with expectation, no binding. Since a nearly athermal character of the reaction (|Δ_r*H*^o| < 3 kJ · mol⁻¹) may be responsible for the insensitivity of ITC, the system was subsequently probed with

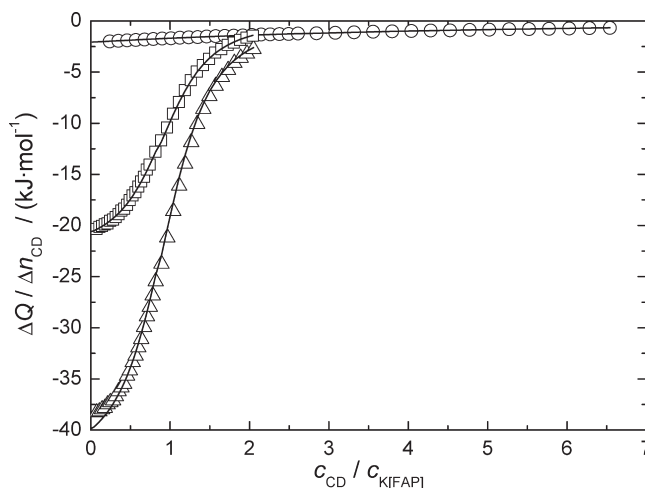


Figure 2. Calorimetric curves for titration of aqueous K[FAP] solution of 0.3 mmol · dm⁻³ with aqueous (○) α-CD of 9.6 mmol · dm⁻³, (□) β-CD of 3 mmol · dm⁻³, and (Δ) γ-CD of 3 mmol · dm⁻³. Solid lines are fits to 1:1 stoichiometry model with parameters given in Tables 1, 2, and 3.

NMR spectroscopy and, in the positive case, the binding constant was determined using the NMR titration.

Thermodynamic quantities for the reactions of the various IL ions examined in this study with α-, β-, and γ-cyclodextrin are presented in Tables 1, 2, and 3, respectively. Results from the literature for the reactions of these and some additional ions with the natural CDs are also given in Tables 1–3 for comparison. The tables are organized in the order of the descending *K* values, to provide an easy overview of the binding affinity scale.

3.2. Comparison with Existing Literature Data. There are only few possibilities for direct comparison of the ion-CD binding parameters obtained in this work to literature values. Moreover, the comparison must be confined to the binding constant only, since no relevant Δ_r*H*^o values are available in the literature. Note that in the only ITC study²³ relevant for the comparison the measured values of Δ_r*H*^o were not reported.

Going through Tables 1–3, one can see that the present calorimetric values *K* = 14 ± 1 for α-CD + Tos⁻, *K* = 90 ± 4 for β-CD + BPh₄⁻, and *K* = 107000 ± 4300 for γ-CD + BPh₄⁻, are in excellent agreement with the respective literature values *K* = 17 ± 5,⁴² *K* = 77 ± 7,⁴³ and *K* = 108000 ± 4300⁴³ (the last two obtained by capillary electrophoresis). Also, our *K* = 3340 ± 140 for the interaction of β-CD with Tf₂N⁻ shows an excellent agreement with *K* = 3200 of Amajjahe and Ritter²³ (ITC) and a fairly good agreement with the values *K* = 3000 (competitive fluorescence) and *K* = 2900 (¹⁹F NMR) of He et al.²⁵ whereas the value of *K* = 1500 obtained by He et al.²⁵ from their conductivity measurements appears in the light of the previous accord doubtful. For the interaction of Tf₂N⁻ with α-CD and γ-CD our values of *K* = 98 ± 10 and *K* = 305 ± 2 are, respectively, four times and two times higher than those measured by Amajjahe and Ritter (*K* = 25 and *K* = 170)²³ with the IL [C₄VIm][Tf₂N]. As concerned this discrepancy, we suspect that the literature values might be those in error since low solubility of [C₄VIm][Tf₂N] prevents ITC experiments from being conducted properly according to the recommendations of Turnbull and Daranas⁴⁴ and Tellinghuisen^{45,46} for lower binding affinity systems (*K* ≤ 300). The present *K* = 3430 ± 24 for α-CD + C₈C₁Im⁺ is 3-fold higher than the electrophoretically measured *K* = 1150 ± 70 of Francois et al.²² Since the present result is in reasonable agreement with

Table 1. Equilibrium Constants K , Standard Enthalpies $\Delta_r H^\circ$, and Standard Entropies $T\Delta_r S^\circ$ for the Reaction $\text{Ion} + \alpha\text{-CD} \rightarrow [\text{ion} \cdot \alpha\text{-CD}]$ in Water at 298.15 K As Determined in This Work or Reported in the Literature

ion	K	$\Delta_r H^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	$T\Delta_r S^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	reference
$\text{C}_8\text{C}_1\text{Im}^+$	3430 ± 24 1150 ± 70	-24.0 ± 0.2	-3.8 ± 0.1	this work Francois et al. ^{22,a}
$\text{C}_8(\text{C}_1)_3\text{N}^+$	2650 ± 110	-19.3 ± 0.4	0.2 ± 0.1	Sun et al. ^{71,b}
C_8NH_3^+	2376 ± 53	-22.8 ± 0.2	-3.5 ± 0.2	Rekharsky et al. ^{72,b}
$\text{C}_6\text{C}_1\text{Im}^+$	670 ± 2	-20.2 ± 0.1	-4.1 ± 0.1	this work
C_6NH_3^+	389 ± 4	-17.5 ± 0.2	-2.7 ± 0.2	Rekharsky et al. ^{72,b}
$\text{B}(\text{CN})_4^-$	356 ± 17	-28.2 ± 0.5	-13.6 ± 0.3	this work
FAP^-	316 ± 4	-23.4 ± 0.2	-9.1 ± 0.1	this work
TF_2N^-	98 ± 10 25	-23.4 ± 0.2 N.A.	-9.1 ± 0.1	this work ^c Amajjahe and Ritter ^{23,b,d}
PF_6^-	40 ± 5	-25.4 ± 2.8	-16.3 ± 2.8	Godinez et al. ^{53,e}
CF_3SO_3^-	38 ± 10	-8.1 ± 2.2	0.9 ± 2.2	Godinez et al. ^{53,e}
$\text{C}_4\text{C}_1\text{Im}^+$	28 ± 4 17			Francois et al. ^{22,a} Qin et al. ^{73,a}
$\text{C}_n\text{F}_{2n+1}\text{CO}_2^-$ ^f	<25			Saint Aman et al. ^{54,g}
Tos^-	14 ± 1 17 ± 5	-11.3 ± 0.5	-4.8 ± 0.4	this work Bergeron ^{42,h}
$\text{C}_4\text{F}_9\text{SO}_3^-$	11 ± 1	-34.6 ± 2.5	-28.7 ± 2.3	this work
BPh_4^-	$\approx 0^i$	$\approx 0^i$		this work

^a Capillary electrophoresis. ^b Isothermal titration calorimetry. ^c ¹⁹F NMR. ^d Measured for $[\text{C}_4\text{VIm}][\text{TF}_2\text{N}]$. ^e Isothermal flow mixing calorimetry. ^f For $3 \leq n \leq 9$. ^g Conductometry. ^h Secondary reference, experimental method not indicated. ⁱ Interaction calorimetrically not detected.

$K = 3610$ (¹H NMR)⁴⁷ for $\alpha\text{-CD} + \text{octyltrimethylammonium}$ ($\text{C}_8(\text{C}_1)_3\text{N}^+$) cation, we consider the value of Francois et al.²² incorrect.

4. DISCUSSION

4.1. General Considerations and Approach. The complexation of ligands to cyclodextrins is generally considered to occur via the inclusion of the hydrophobic part of the ligand into the CD cavity with the polar or charged moiety of the ligand remaining exposed to the aqueous solvent at the wider end of the cavity. A simultaneous and often cooperative action of hydrophobic effects, van der Waals forces and, in some cases, also hydrogen bonding between the ligand and the cyclodextrin provides the resulting drive of the complexation. The guest–host binding affinity can be thus considered as a result of the thermodynamic interplay of several partial processes accompanying the binding. The most important contributions are believed to stem from (a) dehydration of the guest molecule and the CD cavity and (b) van der Waals interactions between the included hydrophobic part of the guest molecule and the cavity. While the dehydration is typically slightly endothermic and entropically gaining, the attractive van der Waals guest–host interactions are characterized by more or less large negative enthalpy changes and, due to a restricted freedom of motion of encapsulated guest molecules, also by more or less large negative entropy changes. The opposed action of enthalpy and entropy in these processes gives the origin to some enthalpy–entropy compensation for the cyclodextrin binding reactions. The hydrophobic interaction corresponding to the combination of processes a and b is generally regarded to be the major driving force of cyclodextrin inclusion binding.

Another prerequisite for any appreciable inclusion binding is a reasonable size match between the guest molecule and the cavity

of cyclodextrin host. Clearly, while an oversized guest cannot be fully accommodated in the host cavity, an oversized cavity does not permit van der Waals forces (which are critically dependent on the distance of separation) to hold the guest in the cavity. Hence, the size-fit concept predicts the highest complex stabilities for the best size-matched host–guest pairs and, on the other hand, a size mismatch of the guest molecule and the cyclodextrin cavity can often well account for a low or even absent complex formation affinity observed for some pairs.

In the following we will be using the concepts of host–guest size matching and the hydrophobic interaction, in order to rationalize the observed widely different affinity of the IL ion-CD pairs to form inclusion complexes. Although definitely simplistic, such an approach has been widely recognized to provide an efficient tool with which one can qualitatively account for the majority of thermodynamic data on cyclodextrin binding. To judge the size proportions of the IL ion-CD pairs in this work, we considered the following well-established dimensions of cyclodextrin cavities: the depth 7.9 Å and the internal diameter ranging from 4.5 to 5.3 Å for $\alpha\text{-CD}$, from 6.0 to 6.5 Å for $\beta\text{-CD}$, and from 7.5 to 8.3 Å for $\gamma\text{-CD}$.⁴⁸ The geometry of guest ions was obtained using a simple MM2 geometry optimization in Hyperchem,⁴⁹ van der Waals radii values of atoms⁵⁰ and visualization in Chem3D.⁵¹ Possible structures of several complexes are shown in Figure 3. The ion-CD binding was further explored through visualized molecular dynamics simulations using a didactic molecular modeling software Odyssey.⁵² Despite the simplistic character of calculations, the simulations carried out both in vacuo and in the aqueous medium provided us with a useful qualitative insight into the mode of binding of individual ion-CD pairs.

4.2. Ion + α -Cyclodextrin Interaction. As seen from Table 1, reactions of $\alpha\text{-CD}$ with IL ions generally exhibit negative $T\Delta_r S^\circ$ values and the complex formation at 298.15 K is enthalpy driven. This finding appears to be quite understandable: as the cavity of

Table 2. Equilibrium Constants K , Standard Enthalpies $\Delta_r H^\circ$, and Standard Entropies $T\Delta_r S^\circ$ for the Reaction $\text{Ion} + \beta\text{-CD} \rightarrow [\text{ion} \cdot \beta\text{-CD}]$ in Water at 298.15 K As Determined in This Work or Reported in the Literature

ion	K	$\Delta_r H^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	$T\Delta_r S^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	reference
$\text{C}_6\text{F}_{13}\text{SO}_3^-$	212000 ± 25100	-35.0 ± 0.3	-4.6 ± 0.1	this work
$\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4\text{SO}_4^-$	167000 ± 6530	-28.8 ± 0.1	1.0 ± 0.1	this work
$\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4(\text{C}_1)_3\text{N}^+$	126000			Patil et al. ^{74,a}
$(\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4)\text{C}_1\text{Im}^+$	76000 ± 1700	-23.3 ± 0.1	4.6 ± 0.1	this work
FAP^-	37200 ± 1840	-43.4 ± 0.4	-17.3 ± 0.3	this work
$\text{C}_6\text{F}_{13}\text{CO}_2^-$	23500 ± 4600			Wilson and Verall ^{55,b}
$\text{C}_4\text{F}_9\text{SO}_3^-$	14420 ± 370	-26.5 ± 0.1	-2.8 ± 0.1	this work
Tf_2N^-	3340 ± 140	-31.8 ± 0.3	-11.7 ± 0.1	this work
	1500			He et al. ^{25,a,c}
	2900			He et al. ^{25,b,c}
	3000			He et al. ^{25,c,d}
	3200	N.A.		Amajjahe and Ritter ^{23,e,f}
$\text{C}_4\text{F}_9\text{CO}_2^-$	2670 ± 440			Wilson and Verall ^{55,b}
FP_2N^-	1610 ± 85	-17.6 ± 0.5	0.7 ± 0.2	this work
C_8SO_4^-	1210 ± 100	-3.6 ± 0.2	14.0 ± 0.2	Eli et al. ^{61,e}
$\text{C}_8\text{C}_1\text{Im}^+$	624 ± 43	-4.3 ± 0.1	11.7 ± 0.1	this work
	672 ± 50			Francois et al. ^{22,g}
FPO^-	546 ± 62	-4.1 ± 0.4	11.5 ± 0.3	this work
$\text{B}(\text{CN})_4^-$	210 ± 2	-23.0 ± 0.1	-9.8 ± 0.1	this work
$\text{C}_6\text{C}_1\text{Im}^+$	90 ± 12^h	$\approx 0^i$		this work ^j
$\text{C}_6(\text{C}_1)_2\text{Im}^+$	112			He et al. ^{25,a}
	159			He et al. ^{25,d}
PF_6^-	120 ± 1	-22.0 ± 0.1	-10.1 ± 0.1	Rak et al. ^{26,e}
	85 ± 5	-22.2 ± 0.9	-11.2 ± 0.9	Godinez et al. ^{53,k}
Tos^-	112 ± 3	-14.3 ± 0.3	-2.6 ± 0.1	this work
BPh_4^-	90 ± 4	-9.0 ± 0.3	2.1 ± 0.2	this work
	77 ± 7			Nhujak and Goodall ^{43,g}
	240 ± 25			Johnson and Reinsborough ^{75,d}
CF_3SO_3^-	57 ± 2	-20.2 ± 0.8	-10.2 ± 0.8	Godinez et al. ^{53,k}
BF_4^-	31 ± 1			He and Shen ^{24,d}
	10 ± 2			Johnson et al. ^{76,d}
$\text{C}_4\text{C}_1\text{Im}^+$	≈ 0	$\approx 0^i$		Rak et al. ^{26,e,j}

^a Conductometry. ^b ¹⁹F NMR. ^c Measured for $[\text{C}_4\text{C}_1\text{Im}][\text{Tf}_2\text{N}]$. ^d Fluorescence displacement method. ^e Isothermal titration calorimetry. ^f Measured for $[\text{C}_4\text{VIm}][\text{Tf}_2\text{N}]$. ^g Capillary electrophoresis. ^h Binding constant evaluated from 2D NMR due to signal overlapping. ⁱ Interaction calorimetrically not detected. ^j ¹H NMR. ^k Isothermal flow mixing calorimetry.

α -CD is relatively narrow, the binding requires a special geometrical guest–host arrangement which on one hand substantially restricts the motional freedom of the involved molecules, but on the other hand leads to their rather tight and energetically very favorable coupling. The highest affinity of α -CD was found to the $\text{C}_8\text{C}_1\text{Im}^+$ cation and further octyl containing cations, followed by a level weaker binding of $\text{C}_6\text{C}_1\text{Im}^+$ and further hexyl containing cations. The diameter of the CH_2/CH_3 group is 4.2 Å, which explains well the snuggle fit of the alkyl chain to the α -CD cavity (see Figure 3a) and the greater affinity α -CD to alkyl containing ions compared to other ions. Perhaps, one may only wonder why the binding affinity of α -CD to the octyl containing ions is so greater than that to the hexyl containing ones, considering that the octyl chain length (10.5 Å) exceeds the formal cavity depth (7.9 Å) while the hexyl chain length (8.1 Å) matches it well. In this context it should be noted that a steady increase of the binding affinity with the alkyl carbon number n_C has been observed (for both α -CD and β -CD) to various types of aliphatic guests up to the $n_C = 10$ and this peculiar behavior has been

explained using the concept of “expanded hydrophobic cavity”¹⁷ which assumes that the water molecules in close proximity to the cavity are considerably affected by the hydrophobic nature of the cavity and behave quite differently from those of the bulk water. Certainly, the headgroup of the aliphatic guest plays also its role, but when comparing the present data on complexation of α -CD with alkylimidazolium ions to literature data on complexation of α -CD with alkylammonium and alkyltrimethylammonium cations, this influence appears to be only moderate.

The tetracyanoborate anion is the ionic guest scoring next to the alkyl containing cations in the binding affinity scale of α -CD in Table 1. The tetrahedral structure of $\text{B}(\text{CN})_4^-$ having a sphere envelope with a radius of 4.2 Å allows the inclusion of only one cyano group into the α -CD cavity. The other three cyano groups left outside are positioned at the wider rim of α -CD conus and, as indicated by molecular modeling calculations, interact through hydrogen bonds with the cyclodextrin's hydroxyl groups, stabilizing thus the complex formed. The matching symmetry of $\text{B}(\text{CN})_4^-$ (C_3) and α -CD (C_6) further adds to the stability.

Table 3. Equilibrium Constants K , Standard Enthalpies $\Delta_r H^\circ$, and Standard Entropies $T\Delta_r S^\circ$ for the Reaction $\text{Ion} + \gamma\text{-CD} \rightarrow [\text{ion} \cdot \gamma\text{-CD}]$ in Water at 298.15 K As Determined in This Work or Reported in the Literature

ion	K	$\Delta_r H^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	$T\Delta_r S^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	reference
BPh ₄ [−]	107000 ± 4300	−43.9 ± 0.2	−15.2 ± 0.1	this work
	108000 ± 6000			Nhujak and Goodall ^{43,a}
FAP [−]	35300 ± 450	−22.5 ± 0.1	3.5 ± 0.2	this work
FP ₂ N [−]	13200 ± 620	−21.9 ± 0.3	1.6 ± 0.1	this work
C ₆ F ₁₃ CO ₂ [−]	420 ± 40			Guo et al. ^{64,b}
C ₆ F ₁₃ SO ₃ [−]	320 ± 30	≈ 0 ^c	14.3 ± 0.3	this work ^b
Tf ₂ N [−]	305 ± 2	−12.6 ± 0.1	1.6 ± 0.4	this work
	170	N.A.		Amajjahe and Ritter ^{23,d,e}
(C ₆ F ₁₃ C ₂ H ₄)C ₁ Im ⁺	220 ± 20	≈ 0 ^c	13.4 ± 0.3	this work ^b
C ₆ F ₁₃ C ₂ H ₄ SO ₄ [−]	150 ± 15	≈ 0 ^c	12.4 ± 0.2	this work ^b
C ₄ F ₉ SO ₃ [−]	94 ± 8	−2.4 ± 0.2	8.9 ± 0.1	this work
FPO [−]	— ^f	≈ 0 ^c		this work ^b
C ₃ F ₇ CO ₂ [−]	11 ± 2			Guo et al. ^{64,b}
B(CN) ₄ [−]	≈ 0 ^c	≈ 0 ^c		this work

^a Capillary electrophoresis. ^b ¹⁹F NMR. ^c Interaction calorimetrically not detected. ^d Isothermal titration calorimetry. ^e Measured for [C₄VIm][Tf₂N].

^f Binding constant evaluation precluded due to complex precipitation.

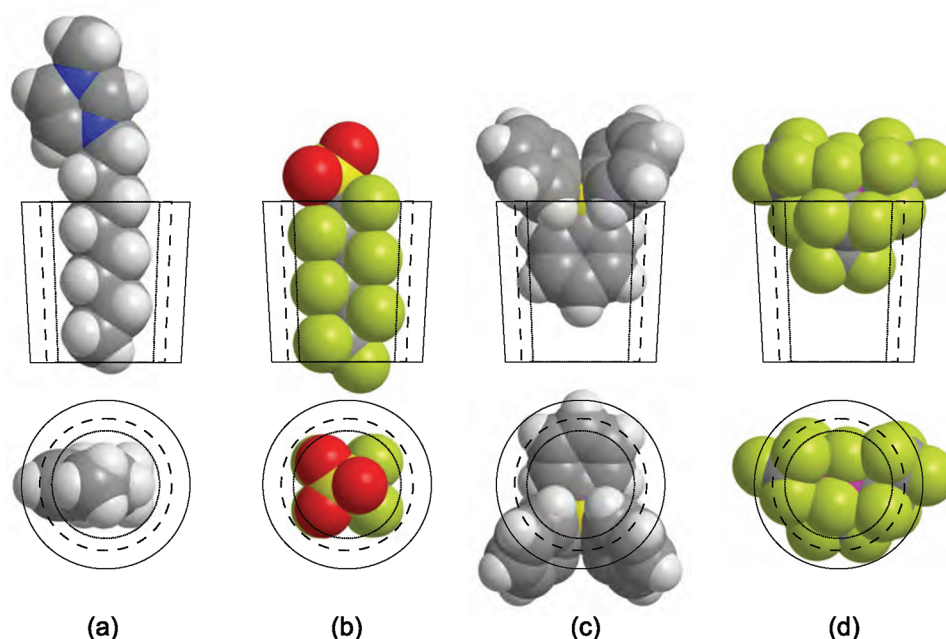


Figure 3. Side and top views on possible structures of ion-CD inclusion complexes: (a) C₈C₁Im⁺; (b) C₆F₁₃SO₃[−]; (c) BPh₄[−]; (d) meridional FAP[−]. Atom identification: white, hydrogen; gray, carbon; red, oxygen; yellow, sulfur, boron; green, fluorine; blue, nitrogen; magenta, phosphorus. Lines are schematic CD cavities with dimensions from Saenger et al.⁴⁸ (---) α-CD; (— · —) β-CD; (—) γ-CD.

From values of binding constant for C₄F₉SO₃[−] and Tf₂N[−] to α-CD obtained in this work and those for CF₃SO₃[−] and for perfluoroalkanoates C_nF_{2n+1}CO₂[−] reported in the literature^{53,54} it is seen, that α-CD exhibits only little affinity to the fluorinated carbon chain. The dimension 6.2 Å of CF₂/CF₃ group prevents the fluorocarbon chain from being accommodated in α-CD cavity even on the wider rim of the CD conus (see Figure 3b) and the interaction occurs via the extracavity association between the α-CD hydroxyls and the −CF₃ group.^{54,55} This weak binding mode should also apply to other fluoroalkyl chain containing ions, namely FPO[−], FP₂N[−], C₆F₁₃SO₃[−], C₆F₁₃C₂H₄SO₄[−], and (C₆F₁₃C₂H₄)C₁Im⁺ ions, and hence their binding to α-CD was

not examined any more. An exception from that is the FAP[−] anion involving besides the CF₂/CF₃ groups also the hydrophobic −PF₃ site for possible inclusion binding. Geometrical considerations reveal that −PF₃ site in the symmetrical (facial) form of FAP[−] can be entirely included in the α-CD cavity and the complex further stabilized via the F · · · H − O − hydrogen bonds between the fluorine atoms of the −C₂F₅ and hydroxyl groups on the wider CD rim and the guest–host symmetry match like in the case of B(CN)₄[−]. Unfortunately, this hypothesis could not be verified, since a detailed NMR study to resolve the binding mode of FAP[−] anion and the complex geometry was precluded due to the precipitation of the complex in D₂O. This problem was

Table 4. Standard Gibbs Energies $\Delta_r G^\circ$, Standard Enthalpies $\Delta_r H^\circ$ and Standard Entropies $T\Delta_r S^\circ$ at $T = 298.15$ K for the Exchange Reaction $[A \cdot \beta\text{-CD}] + B \rightarrow [B \cdot \beta\text{-CD}] + A$

A	B	$\Delta_r G^\circ/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta_r H^\circ/(\text{kJ} \cdot \text{mol}^{-1})$	$T\Delta_r S^\circ/(\text{kJ} \cdot \text{mol}^{-1})$
PF_6^- ^a	FAP^-	−14.2	−21.3	−7.1
$\text{C}_8\text{C}_1\text{Im}^+$	$(\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4)\text{C}_1\text{Im}^+$	−11.9	−19.0	−7.1
C_8SO_4^- ^b	$\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4\text{SO}_4^-$	−12.3	−25.2	−12.9
$\text{C}_3\text{H}_7\text{OH}^c$	$\text{C}_2\text{F}_5\text{CH}_2\text{OH}^d$	−6.5	−13.9	−7.4
$\text{C}_4\text{H}_9\text{OH}^c$	$\text{C}_3\text{F}_7\text{CH}_2\text{OH}^d$	−8.9	−20.1	−11.2

^aData from Rak et al. ²⁶ ^bData from Eli et al. ⁶¹ ^cData from Rekharsky et al. ⁵⁸ ^dData from Ondo et al. ⁵⁹

encountered not only for $\text{FAP}^- + \alpha\text{-CD}$ complex, but also for $\text{FAP}^- + \beta\text{-CD}$ and $\gamma\text{-CD}$ complexes, and those of FPO^- , FP_2N^- with β - and γ -CDs.

Binding of the anions bearing the phenyl (BPh_4^-) and tolyl (Tos^-) groups, moieties too large for the $\alpha\text{-CD}$ cavity (see Figure 3c), are very weak and for the former ion we were even not able to detect it.

4.3. Ion + β -Cyclodextrin Interaction. The diameter of $\beta\text{-CD}$ cavity is greater than that of $\alpha\text{-CD}$ and thus $\beta\text{-CD}$ can offer the possibility of inclusion to a wider range of potential guests than $\alpha\text{-CD}$ does. In particular, guest ions containing fluoroalkyl chains which were observed not to bind effectively to $\alpha\text{-CD}$ exhibit now an extremely strong binding affinity to $\beta\text{-CD}$. As seen from Table 2, among the ions studied, $-\text{C}_6\text{F}_{13}$ bearing ions show the absolutely strongest binding, their binding constants attaining values of 10^5 of the order of magnitude. Figure 3b shows the perfect fit of the $-\text{C}_6\text{F}_{13}$ chain to the $\beta\text{-CD}$ cavity which is considered to be the major stabilizing factor of respective complexes. The notable $K = 2.12 \times 10^5$ we determined for the interaction of $\text{C}_6\text{F}_{13}\text{SO}_3^-$ with $\beta\text{-CD}$ is probably the second highest binding constant ever observed with natural CDs in water, the higher being only $K = 4.15 \times 10^5$ recently determined for a biochemical, bile acid salt tauro- β -muricholate with $\beta\text{-CD}$.⁵⁶ Since shortening the fluoroalkyl chain diminishes the area of its contact with the $\beta\text{-CD}$ cavity, it is obvious that the binding affinity of $\text{C}_n\text{F}_{2n+1}$ bearing guests to $\beta\text{-CD}$ considerably reduces when n decreases: going from $\text{C}_6\text{F}_{13}\text{SO}_3^-$ to CF_3SO_3^- , the binding constant drops almost 4 orders of magnitude.

A closer inspection of thermodynamic quantities of binding of $-\text{C}_6\text{F}_{13}$ bearing ions to $\beta\text{-CD}$ and molecular modeling calculations indicate that it is not only the well size matching inclusion of the fluorocarbon chain into the $\beta\text{-CD}$ cavity but also the head-group type that has a strong impact on the complex stabilization. Going from $\text{C}_6\text{F}_{13}\text{SO}_3^-$, the decrease in the binding affinity upon the headgroup change in $-\text{C}_6\text{F}_{13}$ containing ions is accompanied by the decrease of the exothermicity of the reaction and an increase of the reaction entropy. Comparison of the presently measured values of K for $\text{C}_n\text{F}_{2n+1}\text{SO}_3^-$ ($n = 4, 6$) and the literature ones for $\text{C}_n\text{F}_{2n+1}\text{CO}_2^-$ ($n = 4, 6$)⁵⁵ in Table 2 shows that the change of the headgroup from $-\text{SO}_3^-$ to $-\text{CO}_2^-$ leads to a change in the stability of the complex as large as an order of magnitude. Moreover, the evaluated CF_2 increments in the Gibbs energy of binding, $\Delta\text{CF}_2(\Delta_r G^\circ)$, $-3.3 \text{ kJ} \cdot \text{mol}^{-1}$ and $-2.4 \text{ kJ} \cdot \text{mol}^{-1}$ for $\text{C}_n\text{F}_{2n+1}\text{SO}_3^-$ and for $\text{C}_n\text{F}_{2n+1}\text{CO}_2^-$, respectively, suggest still further stability gain of sulfonate over carboxylate complexes with the prolongation of the perfluoroalkyl chain. The higher stability of sulfonate complexes compared to that of the carboxylate ones could be rationalized by molecular modeling: one extra oxygen atom of $-\text{SO}_3^-$ group and a closer contact of $-\text{SO}_3^-$ (diameter 6.0 Å) with the $\beta\text{-CD}$ cavity in

comparison with the $-\text{CO}_2^-$ group (diameter 5.5 Å) provide for more efficient hydrogen bonding with peripheral hydroxyl groups of $\beta\text{-CD}$.

Other four anions bearing multiple pentafluoroethyl or trifluoromethyl groups, namely FAP^- , TF_2N^- , FP_2N^- , FPO^- , are seen to bind to $\beta\text{-CD}$ with quite different strengths. Except for TF_2N^- these anions are too voluminous to fit into $\beta\text{-CD}$ entirely. The binding of FAP^- to $\beta\text{-CD}$, which is 1 order of magnitude stronger than that of the others, results probably from the inclusion of just one $-\text{C}_2\text{F}_5$ group of FAP^- in its meridional (unsymmetrical) structure into the cavity while the two $-\text{C}_2\text{F}_5$ groups remaining outside may again stabilize the complex via $\text{F} \cdots \text{H}-\text{O}$ bonds with peripheral hydroxyls of CD. The possible structure of $\text{FAP}^- + \beta\text{-CD}$ complex is shown in Figure 3d. Of the four anions, FPO^- binds to $\beta\text{-CD}$ with the lowest strength, which is consistent with somewhat hydrophilic character of this ion.⁵⁷

The effect of guest fluorination on the stability of their $\beta\text{-CD}$ complexes can be further explored by comparing the values of thermodynamic quantities for the exchange reaction



where A is the less fluorinated guest than B. Table 4 lists the thermodynamic quantities of reaction 4 for three selected ionic guest pairs and two pairs of neutral alkanols.^{58,59} The data in Table 4 clearly demonstrate that (i) increasing the fluorination of the guest molecule markedly increases its binding affinity to $\beta\text{-CD}$ and (ii) the enhanced binding due to fluorination of the guest is enthalpy driven and accompanied by entropy loss compensating up to 50% of enthalpy contribution to the complex stabilization.

The complex of $\text{B}(\text{CN})_4^-$ with $\beta\text{-CD}$ was found to be less stable than that with $\alpha\text{-CD}$. As indicated by molecular simulations it is a result of two concurrent effects contributing to the complex stabilization: while the deeper inclusion of $\text{B}(\text{CN})_4^-$ into $\beta\text{-CD}$ cavity increases the guest–host hydrophobic interaction it simultaneously diminishes the possibility for H-bonds formation between them (two H-bonds with $\alpha\text{-CD}$ vs just one with $\beta\text{-CD}$).

As concerns alkylimidazolium cations, their binding affinity to $\beta\text{-CD}$ is appreciably lower than that to $\alpha\text{-CD}$ and in general could be assessed as rather weak. The reason is that the diameter of CH_2/CH_3 groups (4.2 Å) is substantially smaller than the diameter of the $\beta\text{-CD}$ cavity (from 6 to 6.5 Å) and thus the alkyl chain is held in it quite loosely. These conclusions should then apply also to other alkyl containing guests and can be proved by various results from the literature, e.g., for alkyl sulfates,^{60,61} alkanesulfonates,^{60,62} and various uncharged alkylated molecules.¹⁷

A rather weak binding to $\beta\text{-CD}$ was also observed for BPh_4^- and Tos^- anions, although upon complexation their aryl groups (phenyl and tolyl, respectively) can be entirely accommodated in

the β -CD cavity. The observed binding constants are very similar to those reported in the literature⁶³ for benzene ($K = 120 \pm 10$) and toluene ($K = 140 \pm 10$), respectively.

4.4. Ion + γ -Cyclodextrin Interaction. As seen from Table 3, a characteristic feature of the binding of studied ions to γ -CD is the entropy gain upon binding which was observed for all ions but BPh_4^- . This finding suggests that the spacious cavity of γ -CD provides for most included ions still considerable freedom of movement. The bulky BPh_4^- anion leads the binding affinity scale of γ -CD and exhibits the most exothermic binding of all those examined in this work. The binding constant of BPh_4^- to γ -CD attains an order of magnitude value 10^5 , this complex being thus probably the most stable complex of the natural γ -CD ever found. Nhujak and Goodall⁴³ proposed that the tetrahedrally arranged BPh_4^- anion can be completely included into the γ -CD cavity. However, as we determined in this work, the distance of the para positioned hydrogen from the boron atom is 5.6 Å and that between the two para hydrogens of phenyl rings 8.5 Å, which clearly shows that the γ -CD cavity (allowing even its slight deformations) cannot fully accommodate more than two phenyl rings. A probable arrangement of the $\text{BPh}_4^- + \gamma$ -CD complex emerging from our molecular modeling is shown in Figure 3c. In this arrangement the complex appears to be stabilized via $\pi \cdots \text{H}-\text{O}$ interaction between the π -system of phenyl ring and hydroxyl groups on the wider rim of γ -CD cavity.

Two bulky fluorinated anions FAP^- and FP_2N^- score next in the γ -CD binding affinity scale. Both these ions exhibit a high level of binding affinity with order of magnitude values of binding constants 10^4 . Their binding to γ -CD is strongly exothermic and accompanied by only small increase of entropy. It is noteworthy that when performing the molecular simulations on complex formation of BPh_4^- , FAP^- , and FP_2N^- anions with γ -CD, the cavity adjusted appreciably to the guest molecule, where the deformation from rigid circular cone to elliptical one was most pronounced for the $\text{BPh}_4^- + \gamma$ -CD complex.

Longer fluoroalkyl chain ions and the smaller and less fluorinated Tf_2N^- anion show a much lower level of binding affinity to γ -CD. Because of a nearly athermal character of the binding of fluoroalkyl ions to γ -CD, ITC experienced sensitivity difficulties and thus the binding constants for most linear fluoroalkyl chain ions had to be measured by ^{19}F NMR. The measured binding constants for $\text{C}_4\text{F}_9\text{SO}_3^-$, $\text{C}_6\text{F}_{13}\text{SO}_3^-$, $\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4\text{SO}_4^-$, and $(\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4)\text{C}_1\text{Im}^+$ ions range from 90 to 320 and are roughly of the same magnitude as those reported in the literature for $\text{C}_n\text{F}_{2n+1}\text{CO}_2^-$ (with $3 \leq n \leq 6$).⁶⁴ All these findings are consistent with a picture of loose geometric coupling of linear fluoroalkyl chains to the large γ -CD cavity (see Figure 3b).

The ions not listed in Table 3 exhibit no or only very little affinity to form inclusion complexes with γ -CD, because the volume of these ions is too small for the oversized γ -CD cavity. Therefore, interactions of these ions (Tos^- , PF_6^- , and $\text{C}_n\text{C}_1\text{Im}^+$) with γ -CD were not further quantitatively studied. Note that for $\text{C}_n\text{C}_1\text{Im}^+$ with $n < 10$ ions Francois et al.²² have detected no binding. As revealed from the molecular simulations and calorimetric measurements the $\text{B}(\text{CN})_4^-$ with γ -CD belongs also to this category of interactions.

4.5. Enthalpy–Entropy Compensation. A compensatory relationship between enthalpy and entropy changes has been observed for a wide variety of reactions and equilibria and its existence has been convincingly demonstrated also for the inclusion complexation with natural cyclodextrins.^{17,65} In their enthalpy–entropy compensation analysis, Inoue et al.⁶⁵

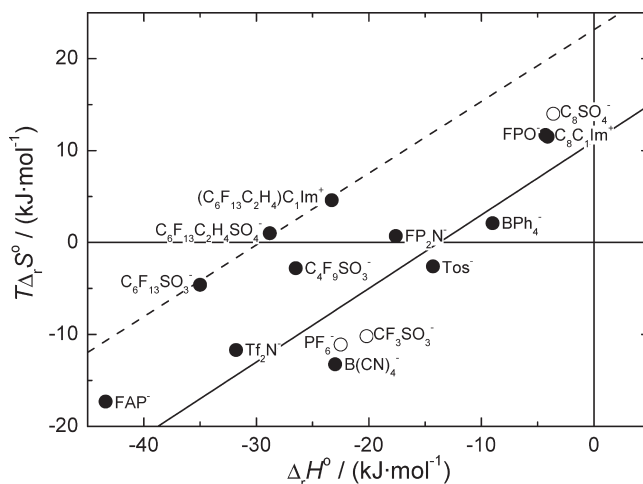


Figure 4. Enthalpy–entropy compensation plot for the reactions $\text{ion} + \beta\text{-CD} \rightarrow [\text{ion} \cdot \beta\text{-CD}]$ in water at 298.15 K. Data from this work: (●) experimental points; (---) linear fit through $\text{-C}_6\text{F}_{13}$ ions. Data from literature: (—) fit of 488 literature data points for β -CD;¹⁷ (○) PF_6^- from Rak et al.,²⁶ CF_3SO_3^- from Godinez et al.⁵³ and C_8SO_4^- from Eli et al.⁶¹

considered $T\Delta_rS^\circ$ to be linearly correlated with the Δ_rH° according to

$$T\Delta_rS^\circ = \alpha\Delta_rH^\circ + T\Delta_rS_0^\circ \quad (5)$$

and proposed the slope α and the intercept $T\Delta_rS_0^\circ$ to be interpreted as measures of conformational changes and the desolvation upon complexation, respectively. Figure 4 shows the enthalpy–entropy compensation plot for studied reactions of IL ions with β -CD; analogous plots for α -CD and γ -CD are not presented owing to limited number of relevant data. In Figure 4 plotted are also additional literature data on complexation of β -CD with three other ions commonly involved in ionic liquids, PF_6^- ,²⁶ CF_3SO_3^- ,⁵³ and C_8SO_4^- ,⁶¹ and the global fit of β -CD binding data (488 data points, $\alpha = 0.80$, $T\Delta_rS_0^\circ = 11 \text{ kJ} \cdot \text{mol}^{-1}$) presented by Rekharsky and Inoue.¹⁷ It is seen, that data for most of the ions more or less follow this global fitting line, lying in an approximately $\pm 5 \text{ kJ} \cdot \text{mol}^{-1}$ band around it. Note that the three points greatly outlying in the positive direction belong to the ions with the terminal $\text{-C}_6\text{F}_{13}$ group. A straight line through these points is parallel ($\alpha = 0.78 \pm 0.07$) with a twice larger intercept ($T\Delta_rS_0^\circ = 23.1 \pm 2.2 \text{ kJ} \cdot \text{mol}^{-1}$) as compared to that of Rekharsky and Inoue. This means that the complex stabilizing entropy gain due to desolvation is for $\text{-C}_6\text{F}_{13}$ bearing ions two times larger than that for binding of most other guests to β -CD. The observed anomaly however appears understandable taking into account the enormous hydrophobicity of the $\text{-C}_6\text{F}_{13}$ chain (compare the aqueous mole fraction solubilities of hexane and perfluorohexane at 298 K which are 2×10^{-6} and 5×10^{-9} ,^{66,67} respectively), its large van der Waals surface contact area (160 Å^2 and 220 Å^2 for hexane and perfluorohexane, respectively), and the efficient displacement of water molecules from the β -CD cavity and its close proximity upon the inclusion of the $\text{-C}_6\text{F}_{13}$ chain indicated by molecular modeling. Also, estimations by Abraham Linear Free Energy Relationship correlations⁶⁸ show that the dehydration of fluorocarbons is much more entropically favored than the dehydration of corresponding hydrocarbons (as Abraham descriptors for perfluorohexane are not known,⁶⁸ compare the estimated hydration entropy $T\Delta_{\text{hyd}}S^\circ(298 \text{ K})$ for

perfluorobutane and butane which are $-48.0 \text{ kJ}\cdot\text{mol}^{-1}$ and $-32.8 \text{ kJ}\cdot\text{mol}^{-1}$, respectively). Inspecting further the enthalpy–entropy compensation plot in Figure 4, it appears to be a quite general rule that the more hydrophobic the encapsulated moiety of the ion, the more positive the deviation from the global averaging line of Rekhsarsky and Inoue, and vice versa.

As suggested by Bertrand et al.,⁶⁹ the performance of enthalpy–entropy correlation can be essentially improved by considering the thermodynamic quantities for the transfer reaction of a given guest between two cyclodextrins



The thermodynamic quantities of reaction 6 for some IL ions and CDs can be calculated by differences of the values given in

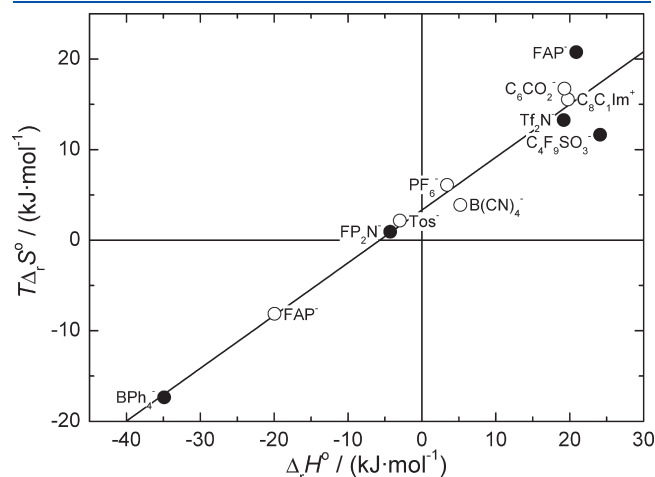


Figure 5. Enthalpy–entropy compensation plot for transfer of ion from $[\text{ion}\cdot\text{CD}(1)]$ to $[\text{ion}\cdot\text{CD}(2)]$ complex: (○) $\alpha\text{-CD} \rightarrow \beta\text{-CD}$; (●) $\beta\text{-CD} \rightarrow \gamma\text{-CD}$; data for C_6CO_2^- from Rekhsarsky et al.⁷²

Tables 1–3. This combination suppresses the effects of hydration of the free ions, and the difference in hydration of the two cyclodextrins is constant. The corresponding enthalpy–entropy compensation plot is shown in Figure 5. Note that it includes data for the ion transfer both from $\alpha\text{-CD}$ to $\beta\text{-CD}$ and from $\beta\text{-CD}$ to $\gamma\text{-CD}$. Yet, the data are compatible and their linear correlation ($\alpha = 0.58 \pm 0.04$, $T\Delta_r S_0^\circ = 3.3 \pm 0.9 \text{ kJ}\cdot\text{mol}^{-1}$) is quite tight ($R = 0.971$, $\text{SD} = 2.8 \text{ kJ}\cdot\text{mol}^{-1}$).

4.6. Beyond the Isolation Strategy: IL-CD Interactions. The isolation method coupled with ITC experiments as applied in this work has proved to be an efficient methodology to characterize the interaction of an individual IL ion with a CD. An alternative procedure for this purpose could however be also considered: ITC experiments are carried out on an IL whose both ions interact appreciably with CD cavity and the ITC data obtained are subsequently analyzed using an appropriate binding model to resolve the effects of cation and anion. An obvious question which then arises concerns the performance and efficiency of the latter procedure.

In order to investigate this issue we have undertaken an additional ITC study on complexation of two PF_6^- ILs, namely $[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6]$ and $[\text{C}_8\text{C}_1\text{Im}][\text{PF}_6]$, with $\alpha\text{-CD}$ and $\beta\text{-CD}$. According to the data obtained for complexation of individual ions with the CDs (see Tables 1 and 2) and indications provided by NMR spectroscopy, the interaction of both ionic moieties of these ILs with the CDs is evident. For each of these IL-CD pairs, our experiments consisted of two or three runs corresponding to different initial concentrations of reactants, the aim being to extend the range of conversion of reactants and provide solid experimental information for the analysis. Two binding models implemented in the MicroCal ITC data analysis software were employed for interpretation of the data: the “Two Sets of Sites” model corresponding to independent binding of cation and anion according to eqs 1 and 2 and the “One Set of Sites” model corresponding to a simplistic IL:CD=1:1 binding scheme. Figure 6 shows results from the titrations of $[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6]$

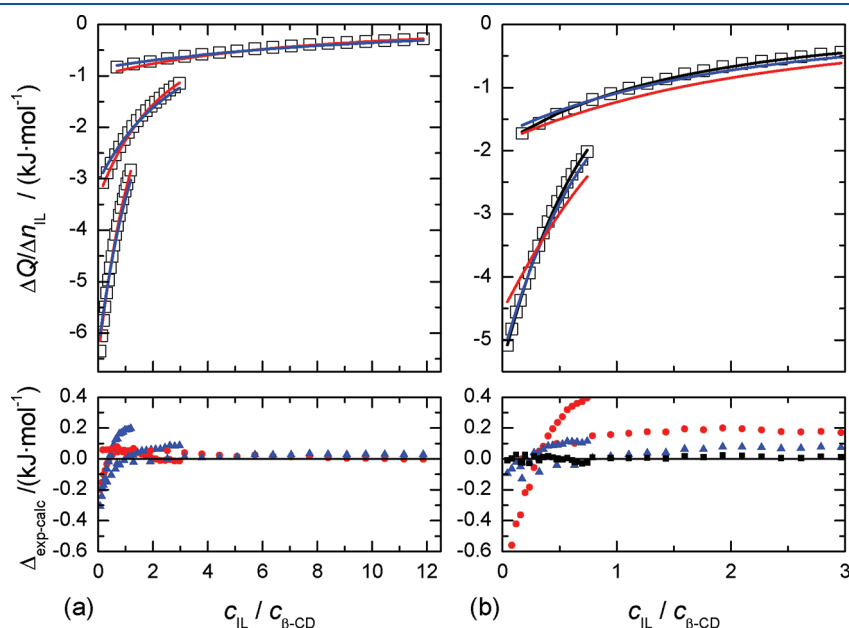


Figure 6. Measured and calculated calorimetric curves (upper row) for titration of aqueous $\beta\text{-CD}$ with (a) $[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6]$ and (b) $[\text{C}_8\text{C}_1\text{Im}][\text{PF}_6]$: (□) experimental points; (black line) fit to “Two Sets of Sites” model; (red line) fit to “One Set of Sites” model; (blue line) simulated titration curves with ion specific parameters obtained by the isolation strategy (Table 2). In lower row plotted are the deviations of the calculated curves by: (■) “Two Sets of Sites” model; (red circles) “One Set of Sites” model; and (blue triangles) simulation, from the experimental data.

Table 5. Equilibrium Constants K and Standard Enthalpies $\Delta_r H^\circ$ for the Reactions of $[C_n C_1 \text{Im}][\text{PF}_6]$ ($n = 6, 8$) ILs with α -CD and β -CD in Water at 298.15 K Determined by ITC Using “Two Sets of Sites” and “One Set of Sites” Models

system	two sets of sites					one set of sites		
	K_1	$\Delta_r H_1^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	K_2	$\Delta_r H_2^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	$s^a / (\text{J} \cdot \text{mol}^{-1})$	K	$\Delta_r H^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	$s^a / (\text{J} \cdot \text{mol}^{-1})$
$[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6] + \alpha\text{-CD}$			failed to converge			497 ± 6	-28.5 ± 0.2	63
$[\text{C}_8\text{C}_1\text{Im}][\text{PF}_6] + \alpha\text{-CD}$	3030 ± 25	-24.2 ± 0.1	12 ± 8	-61.1 ± 42.2	53	2670 ± 56	-25.5 ± 0.2	178
$[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6] + \beta\text{-CD}$			failed to converge			188 ± 8	-17.7 ± 0.4	61
$[\text{C}_8\text{C}_1\text{Im}][\text{PF}_6] + \beta\text{-CD}$	936 ± 75	-4.0 ± 0.1	118 ± 39	-22.9 ± 6.1	16	781 ± 247	-8.8 ± 1.4	272

^a $s = [\sum (\Delta H_{\text{exp}} - \Delta H_{\text{calc}})^2 / (n - p)]^{1/2}$, where n is the number of experimental points, p is the number of adjustable parameters.

and $[\text{C}_8\text{C}_1\text{Im}][\text{PF}_6]$ to β -CD; those for α -CD systems were similar and are not shown. Results from fitting simultaneously these titration curves by the above-mentioned binding models are given for each of the systems studied in Table 5.

As seen, the optimization of the “Two Sets of Sites” model failed to converge for the two $[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6]$ systems where the interaction of one of the ions with the CD cavity is quite weak. Despite substantial experimental information available, four adjustable parameters of the model appear excessive here, inducing thus the fatal instability of the optimization problem. For $[\text{C}_8\text{C}_1\text{Im}][\text{PF}_6]$ systems, where the interaction of the cation with the CD cavity is considerably stronger, the calculation for the “Two Sets of Sites” model converged producing quite small standard deviations of fit. Nevertheless, the fitting was also unstable which manifested itself in a large uncertainty of the calculated values of adjustable parameters K_2 , $\Delta_r H_2^\circ$ for the ion with a weaker binding (PF_6^-). The calculated values of adjustable parameters quite resemble the binding parameters values of individual ions as determined by the isolation method (see Tables 1 and 2), but the agreement is rather semiquantitative.

Looking now at results obtained using the “One Set of Sites” model, it is seen that while this simplistic model gives for the $[\text{C}_8\text{C}_1\text{Im}][\text{PF}_6]$ systems a compromise and much poorer fit than that provided by the physically reasonable model “Two Sets of Sites”, its fitting performance for the $[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6]$ systems is fully adequate. The main problem with the “One Set of Sites” model lies in the interpretation of its parameters which include the effects of both ions. Perhaps, just in systems where the interaction of one of the ions with the CD cavity is significantly stronger than that of the other ion, one can expect that the calculated parameter values should reflect predominantly the stronger interaction. Except for $[\text{C}_6\text{C}_1\text{Im}][\text{PF}_6] + \beta\text{-CD}$ the $\text{C}_n\text{C}_1\text{Im}^+$ cation exhibits a considerably stronger interaction with the CD cavity than the PF_6^- counterion does and comparison of the calculated parameters with the respective ion-specific values in Table 1 and 2 mostly supports the expectation mentioned above. In Figure 6 plotted are also simulated titration curves based on the ion-specific binding parameters from Tables 1 and 2. As seen, the simulations almost perfectly predict the experimental titration curves obtained with ILs. This finding not only indicates that the ion-specific binding parameters obtained by the isolation strategy are truly representative, but also suggests that the binding of individual ions is independent and additive.

Summarizing the gathered experience, we can state that resolving the effect of individual ions from ITC experiments on IL-CD systems is in general a tricky task which cannot be expected to yield precise and reliable results. This conclusion further confirms the superiority of the isolation strategy employed for the purpose throughout this work.

5. CONCLUSIONS

Systematic experimental screening for the binding interaction between hydrophobic ionic moieties of ionic liquids and natural cyclodextrins, as carried out in this work using the isolation strategy and the techniques of isothermal titration calorimetry and NMR spectroscopy, enabled us to establish respective binding affinity scales and to obtain a good insight into the thermodynamics of these systems. To rationalize the observed widely different binding affinities and suggest possible binding modes, the concepts of hydrophobic interaction and guest–host size matching supported by simple molecular modeling proved useful. In some instances, the guest–host hydrogen bonding and/or their mutual geometric symmetry were also found to contribute to the inclusion complex stability. The fluorination of the guest molecule was demonstrated to be a significant factor greatly stabilizing the complexes with β -CD and γ -CD. The stabilities determined for complexes of perfluorohexyl bearing ions with β -CD belong to the highest ever observed with natural CDs in water. The new accurate thermodynamic parameters for ion-CD binding can be helpful for design of supramolecular structuring (e.g., daisy chaining of CDs),⁷⁰ IL-controlled conformational changes of polymers,¹⁴ and CD-controlled solubilization of ionic liquids or salts containing the given ionic moieties.⁴¹

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