

Determination of Binding Constants of Cyclodextrins in Room-Temperature Ionic Liquids by Near-Infrared Spectrometry

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Near-infrared spectrometry has been successfully used to determine association binding constants between phenol and α -, β - and γ -cyclodextrin (CD) in [butylmethylimidazolium][chloride] room-temperature ionic liquid (RTIL). It was found that adding CD into the RTIL solution of phenol resulted in an enhancement in the absorption coefficient of the stretching overtone of the aromatic C–H groups. However, the enhancement induced by CDs in RTIL is much lower (order of magnitude) than those corresponding in D₂O. The binding constants in RTIL are also much lower than those in D₂O ((11 ± 2) , (16 ± 2) , and (40 ± 6) M⁻¹ for phenol and α -, β - and γ -CD, respectively, as compared to 87 and 214 M⁻¹ for α - and β -CD in D₂O). The results obtained seem to suggest that in ionic liquid, the main interaction between phenol and CDs may not be inclusion complex formation but rather external adsorption. A variety of reasons may be responsible for relatively weaker interactions and lower binding constants in the ionic liquid, including differences in the polarity and viscosity of RTIL and D₂O. However, the main reason may be due to the possibility that the 1-butyl-3-methylimidazolium cation of the ionic liquid may form inclusion complexes with CDs either through its imidazolium moiety or its butyl group. Such complex formation would prevent phenol from being included in the cavity of the CDs.

Room-temperature ionic liquids (RTIL) are a group of organic salts that are liquid at room temperature.^{1,2} They have unique chemical and physical properties, including being air and moisture stable, a high solubility power, and virtually no vapor pressure. Because of these properties, they can serve as a “green” recyclable alternative to the volatile organic compounds that are traditionally used as industrial solvents.^{1–4} In fact, RTIL have been successfully used in many applications, including replacing traditional organic solvents in (1) organic and inorganic syntheses;^{5–7} (2) solvent

extractions with crown ethers;⁸ (3) liquid–liquid extractions with supercritical fluid CO₂;^{9–11} (4) electrochemical reactions;^{12,13} and (5) as a medium for enzymatic reactions.¹⁴ Of particular interest are applications of RTIL in analytical chemistry. Specifically, RTIL have been successfully used as matrixes for MALDI-MS,¹⁵ as buffers for capillary electrophoresis^{16,17} and as stationary phases (SP) in gas chromatography (GC).^{18,19} The last application is significant, because it is based on the synergistic exploitation of many advantages of the RTIL, namely, its low vapor pressure and extremely high boiling point and its high viscosity and high solubility power. Interestingly, because of its high solubility power, a variety of additive compounds, including cyclodextrins and their derivatives, can be dissolved in the RTIL-SP to provide additional selectivity and resolution for separations that otherwise are not possible.^{18,19} Successful separations induced by added CDs suggests that there may be interactions between CD and analytes in the RTIL-SP. Unfortunately, because of a lack of method that has the required sensitivity and is suitable for this type of study, to date, the exact nature of the interactions (e.g., inclusion complex formation or electrostatic interactions) is still unknown. Near-infrared (NIR) spectrometry can offer a solution to this problem.

NIR spectrometry has been used extensively in recent years for chemical analysis and characterization.²⁰ The popularity stems from the advantages of the technique, namely its wide applicability and noninvasive, nondestructive and real-time and on-line capabilities. The NIR region covers the overtone and combination transitions of the C–H, O–H, and N–H groups, and since all

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organic and most inorganic compounds possess at least one or more of these groups, the technique can, in principle, be used for analysis of all organic and most inorganic compounds. It is, therefore, reasonable to expect that CDs and RTIL will have strong absorption bands in the NIR region, and as a consequence, their interactions can be spectroscopically investigated using the NIR technique. Additionally, because it has real-time and on-line capabilities that satisfy one of 12 principles of green chemistry,²¹ the NIR technique is suited as a *green method* for the study of the *green solvent*, RTIL. Unfortunately, despite its potentials, the NIR technique has not been widely used to study interactions of CDs in RTIL or in other solvents. The limitation is probably due to the extensive overlap among NIR spectra of different compounds (almost all of them absorb NIR light). High-quality NIR spectra are, therefore, required for subsequent analysis, including background subtraction, deconvolution, and treatment by chemometric methods, such as multivariate methods and partial least-squares methods.²⁰ A NIR spectrometer that has high sensitivity, high light throughput, high stability, and no drift is therefore required. Such a spectrometer was successfully constructed in our laboratory using an acousto-optic tunable filter (AOTF).^{22–24}

The information presented is indeed provocative and clearly demonstrates that it is possible to use the AOTF-based NIR spectrometer to study the interactions between CDs and different analytes in RTIL. Such consideration prompted us to initiate this study, which aims to use the NIR technique to determine association constants between different CDs (i.e., α -, β -, and γ -CD) and aromatic substrates in RTIL as well as in D₂O. Results obtained will help to gain insight into the interactions between CDs and different substrates in RTIL, in general, and in RTIL-SP, in particular.

EXPERIMENTAL SECTION

RTIL 1-butyl-3-methylimidazolium chloride ([BuMIm]⁺[Cl][−]) was synthesized according to procedures previously reported.^{3–7} Specifically, it was prepared by mixing equal molar portions of freshly vacuum-distilled 1-methylimidazole and freshly vacuum-distilled *n*-butyl chloride in a round-bottomed flask equipped with a reflux condenser and dried tube and reacting them for 72 h at 90 °C. The resulting viscous liquid was allowed to cool to room temperature and then was washed three times with dried ethyl acetate (3 × 100 mL). The ethyl acetate layer was decanted. Any ethyl acetate remaining in the ionic liquid was removed by evacuating the ionic liquid under vacuum at 70 °C overnight. The final ionic liquid was kept under either nitrogen or vacuum to protect it from moisture.

It is noteworthy to add that it was previously reported in some publications that [BuMIm]⁺Cl[−] is a solid at room temperature with melting point of 65–69 °C.^{15,17,25–27} We, as well as others,^{18,19}

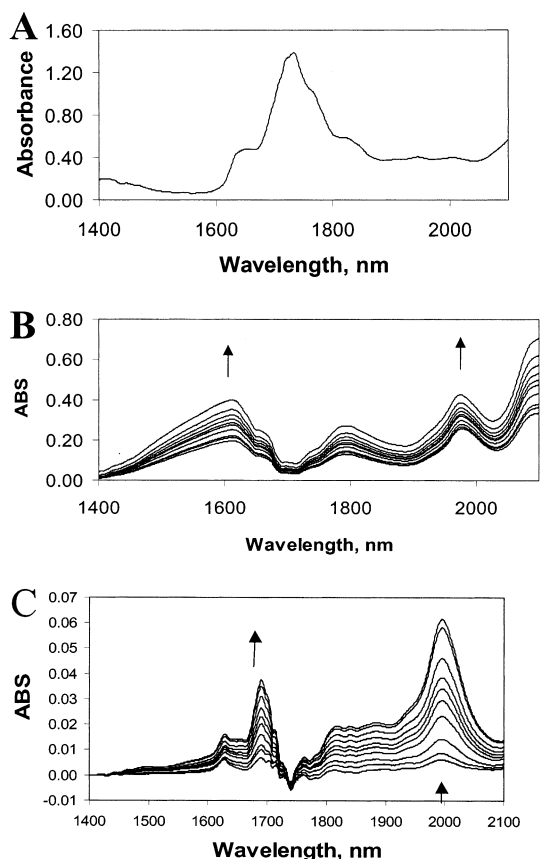


Figure 1. (A) NIR spectrum of butylmethylimidazolium chloride RTIL in 0.5-cm-path-length cell. (B) NIR spectra of different concentrations of γ -CD in [BuMIm][Cl] in 0.5-cm-path-length cell (background absorption of [BuMIm][Cl] was removed). Concentrations of γ -CD (from bottom to top): 0.1037, 0.1120, 0.1217, 0.1333, 0.1474, 0.1556, 0.1647, 0.1750, 0.1867, and 0.2000 M. (C) NIR spectra of different concentrations of phenol in [BuMIm][Cl] in 0.5-cm-path-length cell (background absorption of [BuMIm][Cl] was removed). Concentrations of phenol (from bottom to top): 0.0121, 0.0239, 0.0356, 0.0470, 0.0581, 0.0691, 0.0799, 0.0904, 0.1008, and 0.1110 M.

found that when it was synthesized from freshly distilled methylimidazole and butylchloride, followed by vigorous purification and protection from moisture in the air, [BuMIm]⁺Cl[−] is a clear, pale yellow liquid at room temperature. It remained liquid even when CD or phenol with different concentrations were added. However, it became solid when its temperature was suddenly changed. The exact physical state of [BuMIm]⁺Cl[−] at room temperature is still unclear at this time, but it is possible that it is in a supercooled state.

α -, β -, and γ -cyclodextrins were a gift of Cerestar USA, Inc. NIR spectra were taken on the home-built NIR spectrometer based on an acousto-optic tunable filter. Information on this NIR spectrometer was described in detail in our previous papers.^{11,12} Normally, each spectrum was an average of 30 spectra taken at 1-nm intervals from 1450 to 2450 nm.

RESULTS AND DISCUSSION

The NIR spectrum of RTIL ([BuMIm]⁺[Cl][−]) is shown in Figure 1A. The ionic liquid exhibits several bands at 1638, 1719, and 2150 and a cluster of bands at >2200 nm. The 1719-nm bands and the cluster of bands at >2200 nm (not shown) can be

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Table 1. Molar Absorptivities of Stretching Overtone^a of C-H Groups of Phenol at 1680 nm

compd/media	ϵ (M ⁻¹ cm ⁻¹)
phenol/D ₂ O	0.519 ^b
phenol/ α -CD/D ₂ O	1.219 (135% increase) ^b
phenol/ β -CD/D ₂ O	1.940 (244% increase) ^b
phenol/ionic liquid	0.665
phenol/ α -CD/ionic liquid	0.854 (28% increase)
phenol/ β -CD/ionic liquid	0.884 (33% increase)
phenol/ γ -CD/ionic liquid	0.897 (35% increase)

^a $\Delta\nu = 2$. ^b Values taken from ref 22.

attributed to the overtones and combinations of the aliphatic C-H groups. Overtones and combination transitions of the aromatic C-H groups may be responsible for bands at 1638 and 2150 nm (not shown). Bands at wavelengths longer than 2100 nm were not used in this study, because they have rather high absorption coefficients.

The RTIL ([BuMIm]⁺[Cl]⁻) can dissolve a large amounts of α -, β -, and γ -CD and a variety of aromatic compounds, including benzene, phenol, and chlorophenol. This conclusion was arrived at on the basis of the NIR spectra of the RTIL alone (1A), with γ -CD (1B), and with phenol (1C). Figure 1B shows the absorption spectra of γ -CD at different concentrations (from 0.10 to 0.20 M, with background absorption of RTIL subtracted). As illustrated, γ -CD exhibits a pronounced band at \sim 1970 nm, which can be attributed to the overtones and combination transitions of the O-H groups. Transitions of the aliphatic C-H groups can also be seen at bands at around 1638 and 1850 nm, but they have rather low absorption coefficients, as compared to that of the O-H group. Furthermore, overlap between these bands and those of the ionic liquid makes it difficult to use them for this study.

Absorption spectra of phenol in RTIL at different concentrations, with the contribution of the RTIL subtracted, are shown in Figure 1C. Similarly to the O-H group of the γ -CD, the O-H group of phenol also exhibits a large band at \sim 1950 nm. Additionally, there are several other bands with maximums at \sim 1680 and 1730 nm that can be attributed to transitions of the aromatic C-H groups. The C-H bands may be particularly useful for the determination of inclusion complexes of CDs. This is because we have shown in our earlier study using NIR spectrometry to investigate the inclusion complex formation between phenol, its derivatives, and CD in D₂O²² that upon forming complexes, the oscillator strengths of the C-H stretching overtones [$\Delta\nu = 2$ at \sim 1650 nm] of the aromatic guest compounds were increased by several hundred percent. For instance, as summarized in Table 1, adding α -CD into phenol solution increases the molar absorptivity of the latter by 135% (from 0.519 to 1.219 M⁻¹cm⁻¹), whereas adding β -CD increases it by 244%. The observed increases are rationalized in terms of the enhancement in the inharmonic nature and the libration motions of the guest molecule in the CD cavity.²² The changes in the absorption of this aromatic C-H band upon inclusion complex formation were exploited for the determination of association constants between phenol and α -CD or β -CD, which were found to be 87 and 214 M⁻¹, respectively.²² The results obtained seem to suggest that the stronger the inclusion complexes, the larger the enhancement in

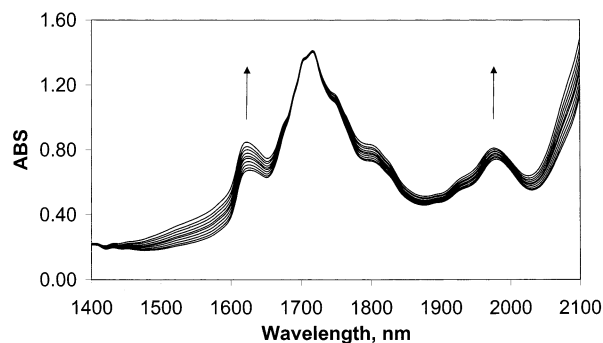


Figure 2. NIR spectra of RTIL solutions containing 0.075 M of phenol and different concentrations of γ -CD in a 0.5-cm-path-length cell. Concentrations of γ -CD (from bottom to top): 0.1037, 0.1120, 0.1217, 0.1333, 0.1474, 0.1556, 0.1647, 0.1750, 0.1867, and 0.2000 M.

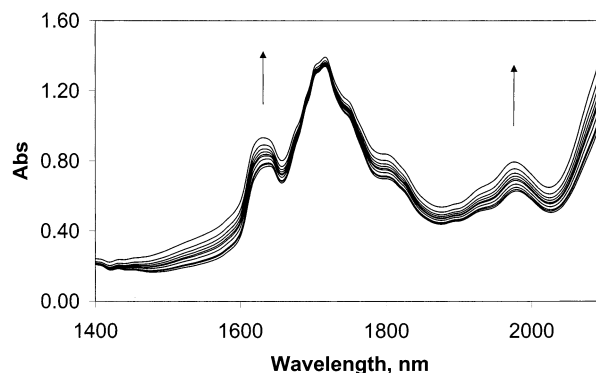


Figure 3. NIR spectra of different concentrations of γ -CD in RTIL in 0.5-cm-path-length cell. Concentrations of γ -CD (from bottom to top): 0.1037, 0.1120, 0.1217, 0.1333, 0.1474, 0.1556, 0.1647, 0.1750, 0.1867, and 0.2000 M.

the oscillator strength of the C-H groups of the aromatic guest compound.

As in the case of D₂O, it was found that in RTIL, the oscillator strength of the C-H groups of phenol was also increased in the presence of α -, β -, or γ -CD. However, the magnitudes of the enhancement are much smaller than those in D₂O; adding α -, β -, or γ -CD to the RTIL solution of phenol increases the ϵ values of the aromatic C-H group by only 28, 33, and 35%, respectively. Because these enhancements are an order of magnitude lower than those in D₂O, it is possible that the interactions between phenol and CDs in RTIL are much weaker and may be of a type different from those in D₂O; namely, the main interaction between phenol and CD may not be inclusion complex formation, but rather, external adsorption.

Subsequently, association constants between phenol and CDs were determined by use of changes in absorption coefficients of the aromatic C-H groups. The measurements were performed by initially recording spectra of a set of RTIL solutions containing 0.075 M phenol and different concentrations of γ -CD (or α - or β -CD with concentrations ranging from 0.104 to 0.20 M) (set 1; Figure 2). Spectra of a second set (set 2) of solutions containing the same γ -CD (or α - or β -CD) concentrations but without phenol were also taken (Figure 3). It is important to point out that spectra in this figure are different from those in Figure 1B. The difference is due to the fact that in Figure 1B, the background contribution of the RTIL was subtracted, whereas all spectra in Figure 3 include

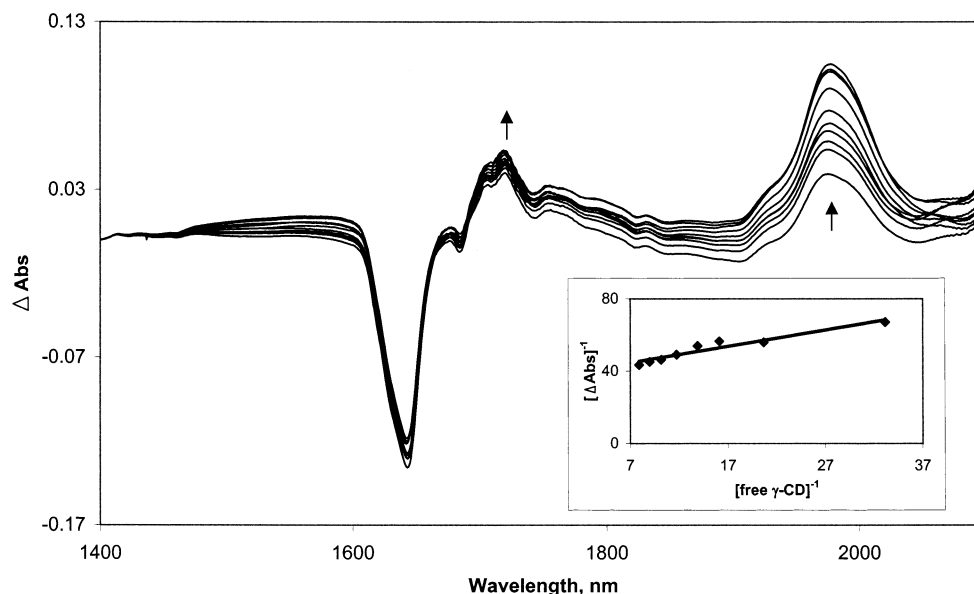


Figure 4. Corrected spectra obtained by subtracting spectrum 2B from spectrum 2A to remove contributions of RTIL and γ -CD. Insert: double reciprocal plot. See text for detailed information.

Table 2. Binding Constants^a of Phenol with α -, β -, and γ -CD in D₂O and in Ionic Liquid

medium	α -CD	β -CD	γ -CD
D ₂ O	87	214	
ionic liquid	11 \pm 2	16 \pm 2	40 \pm 6

^a M⁻¹.

the background absorption of the RTIL. Subtraction of the spectra from set 2 (Figure 3) from those of set 1 (Figure 2) facilitates removal of contribution of RTIL and γ -CD from phenol spectra. The resulting spectra (Figure 4) reflect the absorbance change (Δ Abs) as a function of added host concentration and the dilution effect by the host. Association constants (K_S) were then calculated by linearization of changes in ΔA versus CD concentration using the Benesi-Hilderbrand double reciprocal plot.^{22,28,29} A typical plot of $1/\Delta A$ versus $1/[CD]_{\text{free}}$ is shown in the insert of Figure 4. Initially, $[CD]_{\text{free}}$ was approximated by assuming that there was no free phenol in any solution. Subsequently, $[CD]_{\text{free}}$ was recalculated using the changes in molar absorptivity ($\Delta\epsilon$) value obtained from the intercept of the double reciprocal plot. After several reruns and convergence of $\Delta\epsilon$ and K_S values, the most probable K_S values were selected and listed in Table 2 for α -, β -, and γ -CD. For reference, association constants between phenol and α - and β -CD in D₂O reported in our previous work²² were also listed. Association binding constants for phenol with α -, β -, and γ -CD were found to be (11 \pm 2), (16 \pm 2), and (40 \pm 6) M⁻¹, respectively. These values are much lower than corresponding values of 87 and 214 for α - and β -CD in D₂O.²² The interactions between phenol and CDs are, therefore, much weaker in an ionic liquid than in D₂O.

Taken together, the combination of lower enhancement in the absorption coefficients of the aromatic C–H groups of phenol and

the weaker binding seems to suggest that the nature of the interaction between phenol and CDs in ionic liquid may be different from that in D₂O. The main interaction between phenol and CD may not be inclusion complex formation, but rather, external adsorption. There is a possibility that the 1-butyl-3-methylimidazolium cation of the RTIL may form inclusion complexes with cyclodextrins, through either its imidazolium moiety or its butyl group. Such complex formation will prevent phenol from being included in the cavity of the CDs. In fact, it has been reported that aliphatic hydrocarbons can form inclusion complexes with CDs.³⁰ Imidazole is also known to form inclusion complexes with α - and β -CD, with binding constants of (11.7 \pm 0.2) and (1.9 \pm 1.6) M⁻¹, respectively.³¹ However, it is still unclear if the imidazolium cation can form complexes with CDs.

In summary, it has been demonstrated that interactions between phenol and α -, β -, and γ -CD are relatively weaker in RTIL than in water and that the NIR technique is particularly suitable for the determination of association binding constants for these types of weak interactions.

It was found that adding CD into the ionic liquid solution of phenol resulted in an enhancement in the absorption coefficient of the stretching overtone of the aromatic C–H groups. However, the enhancement induced by CDs in ionic liquid is much lower (an order of magnitude) than the corresponding coefficients in D₂O. The binding constants in an ionic liquid are also much lower than those in D₂O (11 \pm 2, 16 \pm 2, and 40 \pm 6 for phenol and α -, β -, and γ -CD, respectively, as compared to 87 and 214 for α - and β -CD in D₂O). These results seem to suggest that in an ionic liquid, the main interaction between phenol and CDs may not be inclusion complex formation, but rather, external adsorption. A variety of reasons may be responsible for relatively weaker interactions and lower binding constants in an ionic liquid, including differences in the polarity and viscosity of RTIL and D₂O.

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However, the main reason may be due to the fact that the 1-butyl-3-methylimidazolium cation of the ionic liquid may form inclusion complexes with CDs through either its imidazolium moiety or its butyl group. Such complex formation will prevent phenol from being included in the cavities of CDs. In fact, the results obtained in this study confirm the hypothesis proposed in an earlier study¹⁹ in which CDs and their derivatives were dissolved in RTIL-SP for use as chiral selectors in enantiomeric separations by GC.¹⁹ It was found in this study that the number of compounds that were enantiomerically resolved by these RTIL-CD SP is much smaller than those resolved by commercial columns containing the same chiral selectors. The authors speculate that the low resolution may be due to the possibility that interaction between the CD in the RTIL-CD SP and analytes may not have the inclusion complex formation, as in commercial columns, but rather, have external

adsorption.¹⁹ We are currently investigating the possibility of inclusion complex formation of CDs with either the imidazolium moiety or the butyl group of the [BuMIm]⁺ by changing the anion of the ionic liquids from chloride to [BF₄]⁻, [PF₆]⁻, and [Tf₂N]⁻, because it is known that polarity and viscosity of the RTIL are readily changed by their anion.^{1,2} In addition, a similar study will be performed in which the butyl group of the [BuMIm]⁺ cation is replaced with a relatively shorter group, such as ethyl or propane, to reduce the possibility of inclusion complex formation between the CD and the butyl group.

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