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Pressure-controlled high-performance liquid chromatographic study on the influence of rim chemistry on partial molar volume differences between free and complexed cyclodextrins

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Abstract

Pragmatic comparison of pressure dependent retention for differing cyclodextrin rim chemistries is assessed using controlled-pressure HPLC. For pressure differences of <300 bar, systematic shifts in solute capacity factor are observed for both native and methylated β-cyclodextrin stationary phases. In addition to the importance of this observation for the practice of liquid chromatography, this technique can also be implemented in the fundamental determination of the influence of rim chemistry on the cyclodextrin partial molar volume both with and without solute inclusion. That is, pressure-controlled measurements provide a direct comparison between the partial molar volumes for native cyclodextrin (CD) and methylated cyclodextrin (MCD) in the presence and absence of the complexing solute (comp). Surprisingly, direct comparison of the measured partial molar volumes for the two rim chemistries indicates that the presence of neutral solutes does not contribute significantly to the volumetric component of complexation, $V_{comp,CD} - V_{comp,MCD} \approx V_{CD} - V_{MCD}$. In contrast, their ionized counterparts are shown to exhibit marked rim chemistry differences in the partial molar volume of cyclodextrins with and without anion inclusion, $V_{comp(-),CD} - V_{comp(-),MCD} < V_{CD} - V_{MCD}$. Not previously demonstrated by direct chromatographic measurement, these results have interesting implications for advancing the fundamental understanding of host–guest solvation properties.

Keywords: Pressure dependent retention; Cyclodextrin stationary phase; Retention, pressure-dependent; Stationary phases, LC; Nitrophenols; Phenols

1. Introduction

In the 15 years since their introduction [1–3], β-cyclodextrin bonded phases have found extensive use in a variety of different liquid chromatographic applications [4,5]. For cyclodextrin stationary phases, the dominant retention mechanism is inclusion complexation of the solute [1–5]. One key class of interactions in reversed-phase separations is the hydrophobic interactions of the solute with the rigid interior cavity of the cyclodextrin. In addition, solute interactions with the cyclodextrin rims have also been shown to play a significant role in retention and selectivity [4–11]. Accordingly, many investigations have modified the rim chemistry of native β-cyclodextrin as a means of tuning these interactions and thus enhancing selectivity for certain classes of solutes. A variety of derivatized-cyclodextrin station-

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ary phases have been reported in the literature, with permethylation as one of the more common modifications [4–13]. While these modifications are believed to enhance the hydrophobicity of the cyclodextrin, they also clearly result in significant changes in the hydrogen bonding and dipolar interactions of the rim [6]. In these investigations, a methylated β-cyclodextrin stationary phase is utilized which contains methyl groups at the C-2 and C-3 positions on the larger rim of the cyclodextrin. By comparing solute retention on native and methylated β-cyclodextrin stationary phases, the practical and fundamental impact of these changes in rim chemistry may be assessed.

In these studies, the effect of typical chromatographic pressures (10–350 bar) on native and methylated β-cyclodextrin stationary phases is compared. In contrast to temperature studies which elucidate the enthalpic and entropic contributions to retention, pressure studies assess the partial molar volume changes that accompany solute retention (see below). Pressure is an inherent parameter in liquid chromatographic separations, which employ a pressure gradient to induce mobile-phase flow through the column. However, the influence of these modest pressures on reversed-phase separations is often neglected due to the relative incompressibility of polar liquids. Nonetheless, a number of investigators have reported pressure effects on reversed-phase separations using alkylsilane stationary phases [14–18]. Moreover, recent studies in our laboratory have demonstrated pressure-induced perturbations to solute retention on native β-cyclodextrin stationary phases [19–21]. In this paper, pressure-controlled measurements are utilized to elucidate the influence of rim chemistry on the partial molar volume differences of these cyclodextrin complexes. Using this approach, fundamental solvation properties associated with complex formation may be directly assessed. In addition, pressure-induced changes in solute retention are compared for these important stationary phases from a pragmatic perspective.

2. Theoretical background

For the β-cyclodextrin bonded phases of interest in this investigation, the dominant retention mechanism is host–guest complexation with β-cyclodextrin [1–3].

$$\text{solute} + \text{CD} \overset{K_{\text{comp}}}{\rightarrow} \text{solute} \cdot \text{CD} \tag{1}$$

Since both the stationary phase and mobile phase utilized in this study have negligible compressibility at pressures less than 500 bar, pressure-induced changes in retention arise primarily from the pressure dependence of this solute retention equilibrium [19–22]. The change in the equilibrium complexation constant, K_{comp}, with pressure is related through the Gibbs equation to the change in partial molar volume upon complexation (ΔV_{comp}), which represents the difference between the partial molar volume of the solute–cyclodextrin complex and the partial molar volumes of the free cyclodextrin and solute, respectively

$$\Delta V_{\text{comp}} = V_{\text{complex}} - V_{\text{CD}} - V_{\text{solute}} \tag{2}$$

Since partial molar volume represents the change in the volume of a solution as solute is dissolved within it, ΔV_{comp} is quite sensitive to changes in the solvation environment of the solute and cyclodextrin.

Assuming that the phase ratio is invariant with pressure [22], the isothermal change in capacity factor (k) with pressure may then be directly related to the change in partial molar volume upon solute complexation [19–21]

$$\left(\frac{\partial \Delta G_{\text{comp}}}{\partial P}\right)_T = -RT\left(\frac{\partial \ln k}{\partial P}\right)_T + \Delta n\, RT\kappa_S = \Delta V_{\text{comp}} \tag{3}$$

As implied by Eq. (3), capacity factor shifts with pressure are predicted for all solutes that exhibit a change in partial molar volume upon complexation. If solute complexation results in an increase in partial molar volume, an increase in pressure will result in a decrease in capacity factor. Conversely, if there is a decrease in partial molar volume, an increase in pressure will favor complexation and increase k. It is important to note that the change in equilibrium constant, and consequently the capacity factor, with pressure is mediated by a compressibility term. This $\Delta n\, RT\kappa_s$ term accounts for the change in molar concentration due solely to solution compression. In this expression, Δn is the change in stoichiometric coefficients associated with complexation and

κ_s is the isothermal compressibility of the solvent. For the methanol–water (20:80, v/v) mobile phases of interest in this investigation, the isothermal compressibility is $3.83 \cdot 10^{-5}$ bar^{-1} [23] resulting in a value of -0.9 cm^3/mol for this term.

Although complexation equilibria play the dominant role in solute retention on cyclodextrin stationary phases, several studies have shown that ionization equilibria can also have a significant influence on capacity factor [2,7,9,11,19]. In this investigation, the pH of the mobile phase is controlled as a means of assessing the role of rim chemistry on the pressure dependence of capacity factor for differing solute ionization states. For the positional isomers of nitrophenol, the methanol–citrate (20:80, v/v) buffer mobile phase at pH 5 represents a condition under which <1% of the solute is present in the ionized form. When utilizing the unbuffered methanol–water (20:80, v/v) mobile phase (pH 6.6), the ionized fraction (χ_{ioniz}) is increased to 20, 1 and 20% for *ortho*-, *meta*-, and *para*-nitrophenol, respectively. When the mobile phase is changed to methanol–Tris buffer (20:80, v/v) at pH 7.5, the ionized fraction increases to 60, 10 and 70% [19]. Unfortunately, the pH limits of the stationary-phase support do not permit examination of the fully ionized case. Although pressure-induced changes in K_{ioniz} and mobile-phase pH can impact the ionized fraction [24], these changes are too small (<5%) to have a significant impact on retention under these conditions [19]. As a result, these measurements will focus on the pressure-induced equilibrium shift for each rim chemistry as a function of solute and solute ionization state.

3. Experimental

3.1. Chemicals

Nitrophenol and naphthol standards were obtained from Aldrich (Milwaukee, WI, USA) and Sigma (St. Louis, MO, USA), respectively. Mobile-phase solutions were prepared using high-purity methanol (Burdick and Jackson, Muskegon, MI, USA) and distilled, deionized water (Model Milli-Q UV Plus, Millipore, Bedford, MA, USA). For some studies, the aqueous portion was buffered with anhydrous citric acid (Fisher, Fair Lawn, NJ, USA) or Tris[hydroxymethyl] aminomethane hydrochloride (Sigma). The reported mobile-phase pH in all cases is the apparent pH measured in the mixed-solvent mobile phase. All chemicals were used without further purification.

3.2. Chromatographic system

A high-pressure syringe pump (Model 260D, Isco, Lincoln, NE, USA) was used to deliver mobile phase. Probe compounds were dissolved in mobile phase (0.9–1.8 m*M*) and introduced onto a packed capillary column from a 1-μl internal volume injection valve (Valco Instruments, Houston, TX, USA) using the split-injection technique (split ratio = 100±13; $V_{inj} = 10$ nl). A UV–visible absorbance detector (Model UV2000; Thermo Separations, Riviera Beach, FL, USA), fitted with a high-pressure capillary flow cell (76 μm I.D. and 357 μm O.D.; Polymicro Technologies, Phoenix, AZ, USA), was utilized for detection.

For each set of studies, a single, packed capillary column was prepared containing native β-cyclodextrin or 2,3-di-*O*-methyl-β-cyclodextrin bonded stationary phase (Advanced Separations Technology, Whippany, NJ, USA). Preparation of these phases has been described in detail elsewhere [3,10], and both stationary phases employ a 3-glycidoxylsilane spacer arm for attachment to a spherical silica gel support ($d_p = 5$ μm). Moderate pressure (380 bar) was used to pack a fused-silica capillary (251 μm I.D. and 360 μm O.D.) with a slurry of stationary phase and acetone–20 m*M* aqueous NH_4NO_3 (80:20, v/v). The resulting chromatographic columns were terminated using a quartz wool frit at a final column length of 40.4 cm for the β-cyclodextrin column and 44.1 cm for the 2,3-dimethyl-β-cyclodextrin column. In these studies, the use of a capillary column ensured rapid column temperature equilibration with room temperature, which exhibited excellent precision throughout these experiments ($T = 23.5 \pm 0.4$°C).

The pressure-control technique for the chromatographic system has been described in previous work [19]. In brief, the addition of fused-silica capillary at the column inlet and outlet permits the control of average pressure on the column (P_{av}) while main-

taining a constant column flow-rate and pressure gradient across the column. Throughout this study, the column flow-rate was maintained at 1.5±0.02 μl/min, resulting in a column pressure gradient of 90 bar for the native β-cyclodextrin column and 100 bar for the 2,3-di-*O*-methyl-β-cyclodextrin column. Constant flow-rate conditions were confirmed based on the reproducibility of the void time within each study (RSD=2%), which was assessed from the migration of acetone. Elution order of the probes was directly confirmed using single-compound solutions. In addition, solute retention hysteresis was evaluated by direct comparison of capacity factor values at low pressure after high-pressure perturbation. In all cases, low-pressure capacity factor values were statistically identical at the 90% confidence level before and after application of high pressure to the chromatographic column.

4. Results

The rim chemistry of the β-cyclodextrin moiety plays a significant role in the retention of nitrophenols on β-cyclodextrin stationary phases. As shown in Table 1, the capacity factors of *ortho*-, *meta*-, and *para*-nitrophenol are quite different between the native and dimethyl-β-cyclodextrin stationary phases. While these retention differences are most significant for the pH 5 mobile phase where all solutes are present in the neutral form, they are also observed for the pH 7.5 mobile phase where the solutes are present in both ionized and neutral forms. For all three mobile-phase conditions examined, rim-chemistry dependent k results in elution order differences between the native and dimethyl-β-cyclodextrin phases (Table 1). These differences in nitrophenol retention between native and methylated stationary phases are consistent with other reports [11] and most likely result from changes in the strength and type of rim interactions available to the solutes retained on these stationary phases.

For native β-cyclodextrin stationary phases, it has been shown that modest pressure (<350 bar) has a significant effect on the retention of nitrophenols in the neutral state [19,21]. When using a methanol–citrate buffer (20:80, v/v) mobile phase at pH 5, capacity factor decreases ranging from 11 to 12% were observed for a 300 bar increase in pressure [19]. Using the dimethyl-β-cyclodextrin phase, similar capacity factor shifts with pressure (−5 to −12%) are observed for neutral nitrophenols. Since the mobile-phase flow-rate and any concomitant temperature shift have been carefully controlled, these changes in retention are due strictly to the increase in average column pressure. Although pressure is not routinely monitored in HPLC applications, the systematic nature of these shifts suggests that pressure fluctuations may have significant implications for quality control and reproducibility using these stationary phases.

When the mobile-phase pH is increased to induce a higher proportion of ionized nitrophenols, the binding of neutral and ionic solutes to each phase must both be considered (Fig. 1). In comparison to the results at pH 5, the pressure effect on capacity factor using both native and dimethyl-β-cyclodextrin

Table 1
Pressure effect on capacity factors of nitrophenols for different mobile phases with ±values indicating the standard deviation of $n \geq 3$ measurements

P_{av}	k (*ortho*-NP)	k (*meta*-NP)	k (*para*-NP)
Native β-cyclodextrin stationary phase			
47 bar	0.745±0.0038	0.745±0.0038	1.037±0.0016
338 bar	0.665±0.0023	0.665±0.0023	0.910±0.0019
$\Delta k/k$ (%)	−11±0.59	−11±0.59	−12±0.24
2,3-Dimethyl-β-cyclodextrin stationary phase			
55 bar	1.219±0.0051	2.124±0.0049	2.549±0.0065
306 bar	1.154±0.0080	1.91±0.016	2.249±0.0016
$\Delta k/k$ (%)	−5±0.78	−10±0.81	−12±0.26
Native β-cyclodextrin stationary phase			
45 bar	0.240±0.0037	0.854±0.0066	1.17±0.013
324 bar	0.1557±0.00027	0.750±0.0068	0.922±0.0063
$\Delta k/k$ (%)	−35±1.6	−12±1.1	−21±1.2
2,3-Dimethyl-β-cyclodextrin stationary phase			
52 bar	0.244±0.0043	1.55±0.033	0.87±0.018
286 bar	0.156±0.0055	1.386±0.0059	0.679±0.0097
$\Delta k/k$ (%)	−36±2.9	−11±2.2	−22±2.5
Native β-cyclodextrin stationary phase			
42 bar	1.16±0.018	0.99±0.022	3.34±0.036
318 bar	1.07±0.015	0.89±0.016	2.876±0.0094
$\Delta k/k$ (%)	−8±2.0	−10±2.8	−14±1.1
2,3-Dimethyl-β-cyclodextrin stationary phase			
58 bar	1.454±0.0056	2.476±0.0087	2.93±0.020
317 bar	1.35±0.020	2.19±0.031	2.54±0.041
$\Delta k/k$ (%)	−7±1.4	−12±1.3	−13±1.6

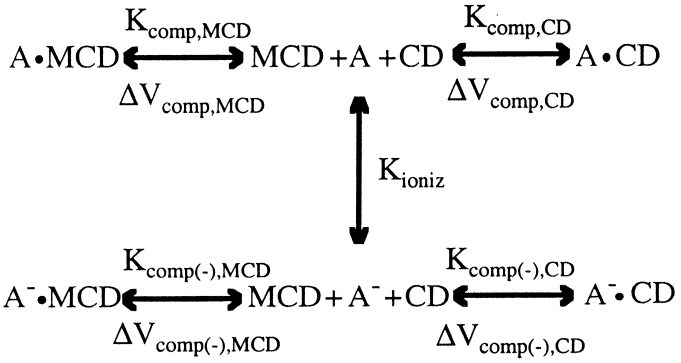

Fig. 1. Schematic diagram of interrelated ionization and complexation equilibria for β-cyclodextrin bonded phase separations.

phase is enhanced for the mixed-ionization case at pH 7.5. Indeed, a 300-bar increase in pressure results in an 11 to 36% decrease in the capacity factor of nitrophenols eluted with a methanol–Tris buffer (20:80, v/v) mobile phase at pH 7.5. Capacity factor shifts are evident from inspection of the chromatograms at high and low pressure (Fig. 2). As with the separations performed at pH 5, the pressure-induced shifts in capacity factor are statistically identical for the native and dimethyl-β-cyclodextrin phases at pH 7.5. These results are somewhat surprising given the fact that the isomeric capacity factors and elution order are quite different for each stationary phase (Table 1).

Since separations using β-cyclodextrin phases utilize both buffered and unbuffered mobile phases, this investigation also examined pressure effects on capacity factor for an unbuffered methanol–water (20:80, v/v) mobile phase. For the native and dimethyl-β-cyclodextrin phases, decreases in capacity factor ranging from −7 to −14% are observed when using this mobile phase. Under these conditions, the *meta* isomer may be used to assess the impact of the buffer on $k(P)$, as there is little change in solute ionization state between the pH 5 buffer and the unbuffered case. As shown in Table 1, the presence of buffer is shown to have little effect on the pressure dependence of capacity factor for the *meta* isomer regardless of rim chemistry. Moreover, even though solute retention is impacted by changes in cyclodextrin rim chemistry, the relative change in retention with pressure does not appear to be affected by the change from native to methylated β-cyclodextrin.

5. Discussion

The comparison of fractional changes in capacity factor with pressure provides an important pragmatic assessment of pressure effects on retention. However, since the cyclodextrin rim chemistry affects k quite significantly (Table 1), it is clear that comparing $\Delta k/k$ between stationary phases convolves rim-chemistry differences in k with differences in the pressure effect on k. For this reason, fundamental evaluation of pressure-induced changes in capacity factor will be considered in terms of the change in partial molar volume upon solute binding with each stationary phase ($\Delta V_{comp,CD}$ and $\Delta V_{comp,MCD}$). Using Eq. (3), the change in partial molar volume upon nitrophenol–cyclodextrin complexation was experimentally determined for each set of conditions. These measurements are compared for the native and methylated β-cyclodextrin in Fig. 3.

When using the methanol–citrate (20:80, v/v) mobile phase, all solutes are present in the neutral form and described by the top equilibria in Fig. 1. Accordingly, the change in partial molar volume upon complexation under these conditions arises solely from $\Delta V_{comp,CD}$ and $\Delta V_{comp,MCD}$. For separations using both the native and methylated β-cyclodextrin phase, the interaction of neutral solutes results in an increase in partial molar volume, ranging from +4.5 to +11.4 cm^3/mol. Although these measurements were made in a methanol–water mixture, the magnitude and sign of ΔV_{comp} are in general agreement with a number of static-pressure measurements for native β-cyclodextrin in aqueous solution [25–28].

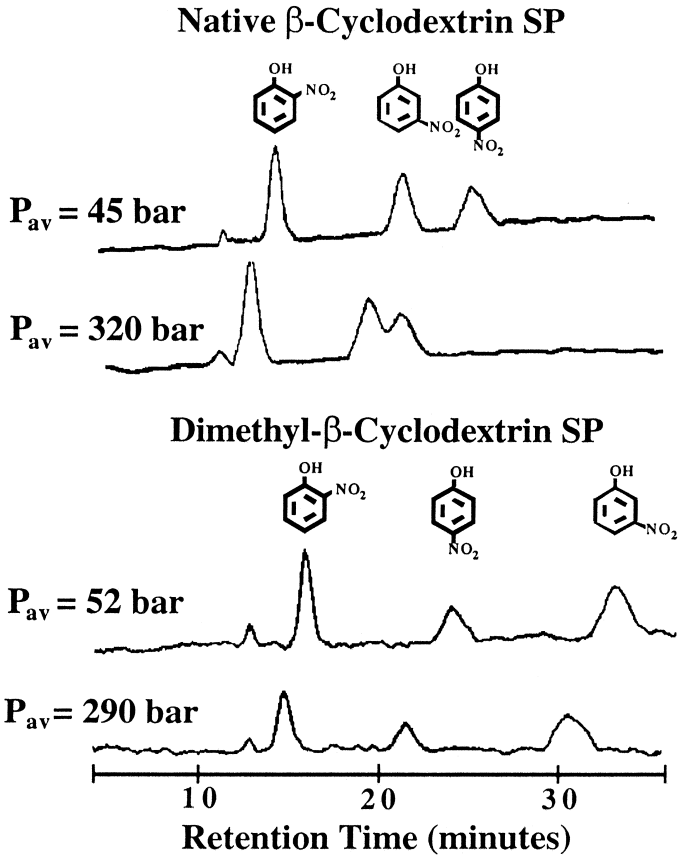

Fig. 2. Pressure effect on the separation of nitrophenol isomers using capillary columns packed with two different β-cyclodextrin bonded phases. Mobile phase was methanol–10 m*M* Tris buffer (20:80, v/v) mobile phase at pH 7.5. Column flow-rate, 1.5 μl/min. The first peak in each chromatogram is the acetone void marker. The retention data for the native β-cyclodextrin has been excerpted in part from Ref. [19].

When the solutes are neutral, comparison of changes in partial molar volume between native and dimethyl-β-cyclodextrin reveals a striking similarity. As shown in Fig. 3, the $\Delta V_{comp,MCD}$ for dimethyl-β-cyclodextrin is statistically identical to $\Delta V_{comp,CD}$ for native β-cyclodextrin complexation with *meta*- and *para*-nitrophenol. Thus, even though the capacity factors are quite different for separations using these two phases (Table 1), the pressure dependence of the capacity factor arises from a ΔV_{comp} of identical magnitude for *meta*- and *para*-nitrophenol. From Eq. (2), this result indicates that for these neutral solutes:

$$V_{comp,CD} - V_{comp,MCD} \approx V_{CD} - V_{MCD} \quad (4)$$

That is, the partial molar volume difference for the complexes is comparable to the partial molar volume difference for the host molecules. This observation is somewhat surprising given the significant differences in rim chemistry and overall cavity length between the methylated and hydroxylated cyclodextrins. Indeed, based on the retention data, the interaction energies for the two rim chemistries with the neutral isomers differ substantially. However, the presence of the neutral solute within the cavity does not appear to play a significant role in the volumetric component of the interaction. For these neutral solutes, solvation differences between the CD and MCD complexes is simply characterized by the solvation differences between the isolated cyclodextrins. Interestingly, the change in partial molar volume of *ortho*-nitrophenol is lower in the MCD

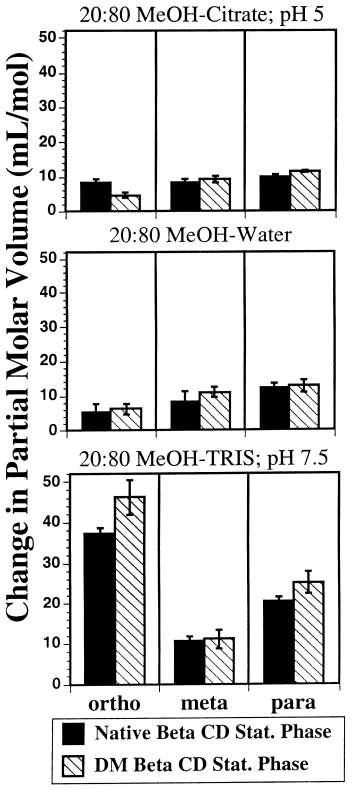

Fig. 3. Change in partial molar volume for the interaction of nitrophenol isomers with native β-cyclodextrin and dimethyl-β-cyclodextrin stationary phases, calculated using the pressure effect on capacity factor and Eq. (3). The change in P_{av} was approximately 300 bar in each case. Each error bar represents the measurement SD from triplicate injections. The retention data for the native β-cyclodextrin has been excerpted in part from Ref. [19].

case (+4.5 cm^3/mol) than in the CD case (+8.7 cm^3/mol). This additional volumetric contribution may arise from perturbations in intramolecular hydrogen bonding upon changing rim chemistries. Studies directly probing the strength of the intramolecular hydrogen bond upon complexation in the methylated and hydroxylated cases are required to further elucidate this mechanism.

For the mixed-ionization state case represented by the pH 7.5 mobile phase (60, 10 and 70% ionized for *ortho*, *meta*, and *para*, respectively), the pressure-dependence of both K_{comp} and $K_{comp(-)}$ must be considered in the overall effect of pressure on retention (Fig. 1). Although the solute ionization state is largely pressure independent for these conditions [19], the pressure dependence of both the neutral and ionized forms must be considered. In this case, the overall change in partial molar volume upon complexation arises from both ΔV_{comp} and $\Delta V_{comp(-)}$. By directly comparing the measured pressure dependence of retention for mobile phases at pH 5 and pH 7.5, the relative magnitudes of ΔV_{comp} and $\Delta V_{comp(-)}$ can be assessed. For both the native and dimethyl β-cyclodextrin stationary phases, the measured ΔV_{comp} for *ortho*- and *para*-nitrophenol more than doubles with a pH increase from 5 to 7.5 (Fig. 3). Although the enhancement of *meta*-nitrophenol is much smaller, this distinction is consistent with the limited ionization of the *meta* isomer under these conditions. Based on the significant increase in the measured ΔV_{comp} with ionized fraction, it is clear that $\Delta V_{comp(-)}$ for the anion is more positive than ΔV_{comp} for the neutral solute. This observation is consistent with electrostriction arguments that predict a smaller partial molar volume for an ion in polar solvent than for its neutral counterpart [24]. As a result, the smaller V_{solute} exhibited in the mixed ionization case for both stationary phases gives rise to a more positive measured ΔV_{comp} with increasing pH (Eq. (2)).

In contrast with the neutral case, when the solutes are partially ionized the measured $\Delta V_{comp,CD}$ and $\Delta V_{comp,MCD}$ are no longer comparable. The presence of ions leads to an observed $\Delta V_{comp,CD}$ that is less than $\Delta V_{comp,MCD}$ (Fig. 3). By analogy to Eq. (4)

$$V_{comp(-),CD} - V_{comp(-),MCD} < V_{CD} - V_{MCD} \quad (5)$$

In contrast with their neutral counterparts, the presence of ionized solutes within the complex appears to play an important role in the volumetric component of these interactions. That is, the solvation differences between the CD and MCD complexes are not simply characterized by the solvation differences between the host molecules. This distinction may arise from a differential solvation environment created upon ion interaction with the hydroxylated and methylated rims. Alternatively, the ionized form may reside at different spatial locations within the cavity depending on the rim chemistry. Either case would create significant differences in the resulting solvated complexes, depending on ion interactions

Table 2
Pressure effect on capacity factors of naphthols eluted with methanol–water (20:80, v/v) with ±values indicating the standard deviation of $n=3$ measurements.

	α-Naphthol	β-Naphthol
Native β-cyclodextrin stationary phase		
k at 42 bar	5.14±0.053	3.47±0.055
k at 318 bar	5.13±0.050	3.43±0.031
$\Delta k/k$ (%)	0±1.4	−1±1.8
ΔV (cm^3/mol)	−1±1.3	0±1.6
2,3-Dimethyl-β-cyclodextrin stationary phase		
k at 67 bar	4.95±0.026	3.86±0.023
k at 301 bar	4.95±0.034	3.77±0.026
$\Delta k/k$ (%)	0±0.9	−2±0.9
ΔV (cm^3/mol)	−1±0.9	1.5±1

with the rim. Again, the *meta* isomer does not exhibit these rim chemistry differences due to minimal ionization under these conditions. As a result, measurements closely resemble the totally neutral case where the ΔV_{comp} is similar for both hosts. Based on these solutes, the pressure dependence of k is only affected by rim chemistry under those conditions where a significant portion of the solute is present in ionized form. This general trend is further corroborated for solutes where the size is more comparable to the cavity inner diameter. In the case of α- and β-naphthol, the pressure dependence of capacity factor for the neutral solutes is minimal (Table 2). Consistent with the smaller nitrophenol isomers, these solutes also exhibit no significant differences in ΔV_{comp} with rim chemistry. Thus, the presence of these neutral model solutes within the CD cavity does not appear to perturb the partial molar volume differences between the hydroxylated and methylated rim chemistries (Eq. (4)). In contrast, the presence of anions within the cyclodextrin cavities leads to significant differences between the differing rim chemistry complexes (Eq. (5)).

6. Conclusions

Pressure-controlled liquid chromatography provides a unique opportunity to measure the volumetric properties of solute complexation. As previously known, the retention of these small aromatic solutes is quite sensitive to changes in cyclodextrin rim chemistry. However, these distinctions in retention behavior do not necessarily result in differences in the fundamental pressure dependence of these interactions. Indeed, cyclodextrin rim chemistry is shown to play no fundamental volumetric role in the pressure effects of complexation for the neutral solutes studied here. In contrast, the change from a hydroxylated to a methylated rim is clearly shown to affect the volumetric differences for the corresponding anion complexes. This distinction between the partial molar volumes of these complexes presents a new view of the solvation process. Shown here for positional-isomer model solutes, this measurement scheme has clear implications for fundamental solvation studies of enantiomeric complexation. Finally, this study further demonstrates the versatility and power of pressure-controlled HPLC to probe the volumetric component of a wide range of interaction chemistries.

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