Study of Retention of Mono-Substituted Phenols in Reversed-Phase Liquid Chromatography Based on the Linear Solvation Energy Relationships Using the Solvatochromic Parameters for Mobile Phases, π_m^*, α_m and β_m

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Retention of mono-substituted phenols in reversed-phase liquid chromatography has been studied based on the linear solvation energy relationships using the solvatochromic mobile phase parameters, π_m^*, α_m and β_m. It has been observed that retention behavior of phenols in RPLC were well represented by regression equations *vs.* solvatochromic mobile phase parameters even though the equations may be incomplete due to lack of an explicit cavity term. Dependence of retention of mono-substituted phenols on the mobile phase properties were varied depending on the type of the organic cosolvent in the mobile phase, e.g., π_m^* and α_m in methanol-water system, but π_m^* and β_m in THF-water system. It has been suggested that retention of phenols in methanol-water system is controlled by the solvophobicity of the mobile phase.

Introduction

Retention in reversed phase liquid chromatography (RPLC) is determined by the difference in various types of interactions which a solute can undergo in the mobile and stationary phase. According to the solvophobic theory of Horvath[1] the stationary phase is considered to be more or less passive. It is now known that the structure and composition of the stationary phase plays an active role in the separation process and has a major effect on selectivity[2,3]. Since RPLC separations are often performed by employing a fixed stationary phase and examining the effect of different mobile phases to obtain optimal separation conditions, understanding the various interactions of solutes with the mobile phase is important for elucidating the retention mechanism and hence the prediction of selectivity in RPLC. There have been many studies of the effect of the mobile phase on retention. Solubility parameter theory[4,5], the interaction index[6], and statistical mechanics[7] have been applied in attempts to better understand the mechanism of retention, but none of these approaches makes quantitative predictions of retention.

Recently the $E_T(30)$ scale of mobile phase polarity[8-10] and linear solvation energy relationship (LSER) based on the Kamlet-Taft multiparameter scales[11,12] were successfully used to study retention in RPLC. Dorsey and coworkers[8] have shown that plots of lnk' for a large number of solutes *vs.* the mobile phases' $E_T(30)$ solvatochromic parameters are very often more linear than are plots of lnk' *vs.* volume fraction of organic modifier. However this approach only allows for the prediction of retention at different mobile compositions to be made, but provides no information about the relative strength of various interactions between a solute and the mobile phase, which are important in understanding the retention process. The $E_T(30)$ scale had been proposed as a single parameter overall scale of solvent polarity, but as Carr[13] recently pointed out, there can be no global single parameter solvent polarity scale except when the solute and solvent are incapable of forming hydrogen bonds.

In contrast LSER approaches based on multiparameter scales[11-13] seek to relate retention in a fixed mobile phase-stationary phase system to variations in the solute properties, or to variations in mobile phase's properties when the solute and stationary phase are fixed. The Kamlet-Taft multiparameter solvent scales are based on the differential evaluation of solvent dipolarity/polarizability (π^*), solvent HB donor acidity (α), and solvent hydrogen bond acceptor basicity (β)[14-17]. Kamlet, Taft and their coworkers have applied these measures of interaction strength based upon linear solvation energy relationships (LSER's) to over 600 processes[18], including a large number of systems of immediate relevance to chromatography, such as Rohrschneider's gas-liquid partition coefficients[19], Snyder's solvent strength scales for normal and reversed phase liquid chromatography[20,21], and retention in reversed phase liquid chromatography[11,12,22].

Thus far the LSER approaches based on multiparameter scale has been applied to relate retention in a fixed mobile phase-stationary phase system to variations in the solute properties[11,12,22]. This paper reports the first correlation of RPLC retention to variations in mobile phase's properties when the solute and stationary phase are fixed. In order to make the difference between the two LSER approaches clear we briefly restate the basis of the LSER formalism when applied to phase-transfer processes. A general solute or solvent property can be correlated via the use of three types of terms as given below[17]:

$$XYZ = XYZ_o + \text{cavity term} + \text{dipolar term} + \text{hydrogen bonding term (s)} \quad (1)$$

The cavity term is usually taken as the product of the solute molar volume and the square of the Hildebrand solubility parameter (δ_H) of the solvent. The dipolar term is the product of the solute π^* and the solvent π^*. The hydrogen bonding terms are written as a cross product of the solute α and the solvent β and and the product of the solute β and the solvent α. In the case of the chromatographic retention, XYZ in the equation below denotes a logarithmic capacity factor and the subscript 2 designates a solute property. The subscripts s and m denote the stationary and mobile phases, respec-

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tively[12].

$$XYZ=XYZ_o+M(\delta_s^2-\delta_m^2)V_i/100+S(\pi^*s-\pi^*_m)\pi_i^*$$
$$+A(\beta_s-\beta_m)\alpha_i+B(\alpha_s-\alpha_m)\beta_i \quad (2)$$

The coefficients M, S, A, and B are the fitting parameters.

When a system with a fixed pair of mobile and stationary phases is considered, eq. 2 is reduced to

$$XYZ=XYZ_o+mV_i/100+s\pi_i^*+a\alpha^2+b\beta_i \quad (3)$$

This equation has been successfully used to correlate the retention of a large number of solutes on a variety of bonded phase columns with several different mobile phase modifiers[11,12,22]. It has been shown based on this equation that retention in RPLC does not depend strongly on solute HB donor acidity. However, the data set excluded strong HB donor solutes such as alcohols, phenols, carboxylic acids, etc. from consideration.

It is known that as the mobile phase composition is varied in RPLC, the stationary phase is modified. However, Ying *et al.*[23] and Dill[24] have recently shown that the modification of the stationary phase due to the change in the amount of the organic cosolvent in the mobile phase is very small and hence the chemical potential of the solute in the stationary phase is affected to only a relatively small degree by the cosolvent over the full range of mobile phase cosolvents. Under this condition, eq. 2 gives the following relationship between the logarithmic capacity factor and the mobile phase properties:

$$XYZ=XYZ_o+m'\delta_m^2+s'\pi_m^*+a'\beta_m+b'\alpha_m \quad (4)$$

Among the mobile phase properties in eq. 4, π^*_m and β_m values are available in the literature[25,26], and α_m values for aqueous mixtures of a number of organic cosolvents have been recently reported by us[27]. Experimental δ_m values are not available for the aqueous mixtures of interest in this study. They may be calculated by the following relationship:

$$\delta_m^2=\phi_w\delta_w^2+\phi_o\delta_o^2+\delta_e^2 \quad (5)$$

where ϕ_w and ϕ_o denote the volume fraction of water and the organic cosolvent, respectively and δ_e is the excess function of δ_H. However, δ_e values are considerably greater than zero for these highly nonideal mixtures and are not experimentally available. An approximate linear relationship between π^* and the square of the solubility parameter has been noted for 17 nonaromatic, nonhalogenated, aprotic liquids[13]:

$$\delta_H^2=44.1+95.6\pi^*$$
$$r=0.858, \quad sd=19.7 \quad (6)$$

If these relationships also hold for aqueous mixtures, two monotonic functions for the mixtures will be likely collinear over a sufficiently narrow range in argument[13]. Under this condition eq. 4 reduces to

$$XYZ=XYZ_o+s''\pi_m^*+a''\beta_m+b''\alpha_m \quad (7)$$

In this work we report the correlations of logarithmic capacity factors for mono-substituted phenols in RPLC with the properties of the mobile phase based on eq. 7 and attempt to provide information about various interactions of the solute with the mobile phase which affect the retention. The retention data for phenols are chosen in this study since phenols are dipolar, acidic and basic in hydrogen bonding (π^*_2, α_2, $\beta_2>0$. see Table 1) and thus allow eq. 7 with all the mobile phase parameters to be applied for correlation. However, as will be shown below, only one or two mobile phase parameters are necessary for describing retention behavior of mono-substituted phenols studied in this work, depending on the type of the organic cosolvent in the mobile phase.

Table 1. Properties of Selected Mono-Substituted Phenols

Substituent	$V_i/100$	π_2^{*a}	β_2^a	α_2^a
m-NH_2	0.607	0.78	0.40	0.58
p-NH_2	0.607	0.73	0.40	0.58
m-OCH_3	0.675	0.78	0.34	0.58
p-OCH_3	0.675	0.73	0.34	0.58
m-CH_3	0.634	0.68	0.34	0.58
p-CH_3	0.634	0.68	0.34	0.58
m-Cl	0.626	0.77	0.23	0.69
p-Cl	0.626	0.72	0.23	0.69
m-NO_2	0.665	1.06	0.23	0.69
p-NO_2	0.665	1.01	0.23	1.00
p-CN	0.635	0.90	0.23	0.69
p-F	0.565	0.73	0.28	0.65
p-Br	0.669	0.79	0.23	0.69
phenol	0.536	0.72	0.33	0.61

[a] Estimated values based on the parameter estimation rules[29]. The values for ortho-isomers can not be estimated by the rules due to the strong intramolecular hydrogen bonding between the substituent and hydroxyl group.

Experimental

The retention data of 20 mono-substituted phenols were measured for methanol-, acetonitrile-, and tetrahydrofuran-water system at a number of different organic cosolvent compositions and were given elsewhere[28]. A μ-Bondapak C-18 Radial pak column (100 × 8 mm, 10 μm, Waters, Milford, MA, U.S.A.) was used throughout the study. The column was placed in a water jacket, and the temperature was controlled at 25 ± 0.2 °C. A HPLC system from Waters (Milford, MA, U.S.A.) composed of a Model 510 pump, a Model U6K injector, a Model 441 UV-detector set to a wavelength of 254 nm and a Model 730 Data Module was used. A 5 to 10 μl sample dissolved in methanol was injected *via* a precision syringe. The eluent flow rate was 2 m*l*/min. Water was used as the void volume marker and the void volume was determined at each mobile phase composition throughout the course of the series of measurements. The mobile phase was prepared by mixing a measured volume of water and the organic cosolvent and degassed before use. The solvatochromic mobile phase parameters over a range of cosolvent compositions were taken from the literature[25-27] and are given in Table 2.

Results and Discussion

In order to gain an understanding of factors affecting re-

Table 2. Solvatochromic Parameters for Mobile Phases

	ϕ_o[a]									
	0.20	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.80
methanol–water											
π_m^*[b]	–	1.11	–	1.08	1.06	1.03	1.01	0.98	0.95	0.91	0.82
α_m[c]	–	1.15	–	1.10	1.08	1.07	1.05	1.04	1.03	1.02	1.02
β_m[d]	–	0.43	–	0.50	0.52	0.53	0.54	0.54	0.55	0.55	0.54
acetonitrile–water											
π_m^*	1.12	1.06	1.02	0.99	0.97	0.95	0.93	0.91	–	0.97	–
α_m	1.08	1.01	0.98	0.95	0.92	0.90	0.90	0.90	–	0.88	–
β_m	0.39	0.41	0.41	0.40	0.40	0.40	0.41	0.41	–	0.44	–
tetrahydrofuran–water											
π_m^*	1.14	1.05	1.00	0.95	0.92	0.89	–	0.84	–	–	–
α_m	0.98	0.90	0.87	0.86	0.84	0.83	–	0.78	–	–	–
β_m	0.52	0.47	0.45	0.43	0.42	0.41	–	0.43	–	–	–

[a]Volume fractions of the organic modifier in mobile phases. [b]Data from ref. 25. [c]Data from ref. 26. [d]Data from ref. 27.

Table 3. Multiple Linear Regression Results for Correlations between lnk′ and Mobile Phase Solvatochromic Parameters with Methanol–Water Mixtures as the Mobile Phase[a]

Solute	–(y-int)	s''	b''	sd	r	CL%
o-NH_2	12.37(0.88)	6.40(0.59)	4.89(1.26)	0.075	0.996	99.5
m-NH_2	14.01(1.29)	6.50(1.63)	5.56(2.58)	0.091	0.993	95.0
p-NH_2	16.91(0.26)	7.39(0.17)	7.49(0.37)	0.022	0.999	99.9
o-OCH_3	16.04(0.64)	6.44(0.43)	9.03(0.91)	0.055	0.999	99.9
m-OCH_3	18.55(0.97)	3.87(0.65)	13.83(1.39)	0.083	0.997	99.9
p-OCH_3	17.12(0.74)	6.72(0.50)	9.51(1.06)	0.064	0.998	99.9
o-CH_3	17.52(0.71)	7.69(0.47)	9.77(1.01)	0.061	0.999	99.9
m-CH_3	18.46(0.84)	4.91(0.57)	13.22(1.21)	0.072	0.998	99.9
p-CH_3	17.57(0.47)	8.48(0.32)	8.99(0.68)	0.041	0.999	99.9
o-Cl	17.29(0.90)	7.49(0.60)	9.79(1.29)	0.077	0.998	99.9
m-Cl	19.80(1.28)	5.22(0.86)	14.67(1.83)	0.109	0.996	99.9
p-Cl	17.63(0.69)	9.66(0.46)	8.36(0.98)	0.059	0.999	99.9
o-NO_2	15.22(0.80)	7.08(0.54)	8.37(1.14)	0.068	0.998	99.9
m-NO_2	18.00(1.02)	5.48(0.69)	12.19(1.46)	0.087	0.998	99.9
p-NO_2	17.01(0.44)	8.94(0.29)	7.84(0.63)	0.038	0.999	99.9
p-SCH_3	19.96(0.50)	8.76(0.34)	11.20(0.72)	0.043	0.999	99.9
p-CN	18.98(0.44)	6.55(0.30)	11.58(0.63)	0.038	0.999	99.9
p-F	16.30(0.43)	6.94(0.29)	8.95(0.62)	0.037	0.999	99.9
p-Br	19.72(0.50)	7.82(0.33)	12.25(0.71)	0.043	0.999	99.9
phenol	14.98(0.44)	8.80(0.30)	5.60(0.64)	0.038	0.999	99.9

[a]The numbers in parentheses are standard deviations in the coefficient estimates.

tention of phenols in RPLC, multiple linear regressions of lnk′ *vs.* solute properties were performed at first based on eq. 2 for selected phenols for 70/30 v% water/methanol system. If the two obvious outliers, *m*- and *p*-nitrophenol, are excluded the resulting correlation is given by eq. (8).

$$\begin{aligned} lnk' = & 9.07\,(\pm 2.74) + 1.92\,(\pm 1.14)\ V_I/100 \\ & - 3.13\,(\pm 0.85)\,\pi_2^* - 5.99\,(\pm 3.01)\,\alpha_2 \\ & - 11.25\,(\pm 2.26)\,\beta_2 \qquad (8) \\ n=12,\ & r=0.975,\ sd=0.127 \end{aligned}$$

where V_I denotes intrinsic molar volume of the solute[30]. It is seen in eq. (8) as might be expected from a priori considerations, that increasing solute size (V_I) causes an increase in retention, *i.e.*, free energy concepts favor solute transfer from the more cohesive mobile phase to the less cohesive stationary phase. Opposing this effect, increases in solute dipolarity (π^*_2), HB donor acidity (α_2) and HB acceptor basicity (β_2) lead to lower log k' values because the solutes have greater affinities for the more polar and hydrogen bonding aqueous mobile phase. The equation indicates that the factors influencing the RPLC properties for phenols become more important in the order, endoergic cavity term ($mV_I/100$)<exoergic dipolar term ($s\pi^*_2$)<solute-to-solvent

Table 4. Linear Regression Results for Correlations between lnk' and Mobile Phase Solvatochromic Parameter π^*_m with Acetonitrile–Water Mixtures as the Mobile Phase

Solute	–(*y*–int)	*s*''	*sd*	*r*
o–NH_2	6.48(0.44)	6.48(0.45)	0.099	0.984
m–NH_2	4.53(0.46)	3.96(0.47)	0.104	0.954
p–NH_2	6.23(0.81)	5.64(0.83)	0.183	0.932
o–OCH_3	6.85(0.26)	7.40(0.27)	0.059	0.995
m–OCH_3	8.06(0.28)	8.58(0.28)	0.062	0.996
p–OCH_3	7.43(0.34)	7.69(0.35)	0.076	0.993
o–CH_3	9.44(0.23)	10.38(0.23)	0.051	0.998
o–CH_3	8.83(0.22)	9.73(0.23)	0.050	0.998
p–CH_3	8.91(0.19)	9.74(0.19)	0.043	0.999
o–Cl	9.86(0.20)	10.92(0.20)	0.044	0.999
m–Cl	10.53(0.19)	11.84(0.20)	0.043	0.999
p–Cl	10.47(0.23)	11.65(0.23)	0.051	0.999
o–NO_2	8.99(0.14)	10.29(0.15)	0.032	0.999
m–NO_2	9.54(0.15)	10.47(0.15)	0.034	0.999
p–NO_2	9.50(0.33)	10.20(0.33)	0.073	0.996
p–SCH_3	10.47(0.22)	11.53(0.22)	0.049	0.999
p–CN	8.04(0.23)	8.48(0.24)	0.052	0.997
p–F	8.25(0.17)	8.93(0.17)	0.038	0.999
p–Br	10.80(0.18)	12.18(0.19)	0.041	0.999
phenol	7.34(0.25)	7.73(0.25)	0.056	0.996

(type B) hydrogen bonding term ($a\alpha_2$)<solvent-to-solute (type A) hydrogen bonding term ($b\beta_2$). This result indicates that all three mobile phase parameters, π^*_m, α_m, and β_m, should be included in the regressions based on eq. (7). However, as described below, only one or two mobile phase parameters are necessary for describing retention behavior of most of mono-substituted phenols studied in this work, depending on the type of the organic cosolvent in the mobile phase.

The results of multiple linear regressions between lnk' for 20 phenols and mobile phase solvatochromic parameters for methanol–, acetonitrile–, and tetrahydrofuran–water mixtures as the mobile phase are given in Tables 3,4, and 5, respectively. Because the polarity, HB acidity and basicity of the mobile phases are quite different depending on the type of organic cosolvent in the mixture, it will be appropriate to examine the regression results by the type of organic modifier in the mobile phase.

Methanol–Water System. Even if the result of regression of retention for phenols *vs.* the solute parameters dictates that all three mobile phase parameters be included in the regression *vs.* the mobile phase parameters, we, based on previous experience, build up the regression in a stepwise fashion in order to avoid addition of unnecessary parameters. For *o*–aminophenol regression of lnk' *vs.* mobile phase dipolarity parameter, π^*_m, for nine different cosolvent compositions, gives the following correlation equation:

$$lnk' = -9.15\,(\pm 0.51) + 8.38\,(\pm 0.51)\,\pi^*_m$$
$$r = 0.987,\quad sd = 0.131 \qquad (9)$$

Since *o*–aminophenol is quite basic in HB and the mobile phase is composed of water and methanol both of which are very acidic in HB (see Table 1 and 2), the HB acidity of mobile phase is included in the regression equation and we obtain:

$$lnk' = -12.37\,(\pm 0.88) + 6.40\,(\pm 0.59)\,\pi^*_m$$
$$+4.89\,(\pm 1.26)\,\alpha_m$$

Table 5. Multiple Linear Regression Results for Correlation between lnk' and Mobile Phase Solvatochromic Parameters with Tetrahydrofuran–Water Mixtures as the Mobile Phase

Solute	–(*y*–int)	*s*''	–*a*''	*sd*	*r*	CL%
o–NH_2	6.01(0.36)	8.58(0.71)	4.73(1.91)	0.072	0.997	95.0
m–NH_2	6.33(0.63)	3.74(1.26)	5.41(3.37)	0.128	0.984	90.0
p–NH_2[a]	6.88(1.07)	6.17(1.10)	–	0.275	0.929	–
o–OCH_3	6.12(0.20)	10.12(0.40)	6.93(1.08)	0.041	0.999	99.9
m–OCH_3	5.89(0.53)	12.31(1.07)	12.01(2.85)	0.108	0.995	99.9
p–OCH_3	6.37(0.29)	15.35(0.54)	18.16(1.45)	0.055	0.999	99.9
o–CH_3	7.83(0.37)	12.21(0.74)	5.88(1.97)	0.074	0.998	95.0
m–CH_3	8.01(0.21)	14.96(0.41)	11.94(1.10)	0.042	0.999	99.9
p–CH_3	7.58(0.23)	11.90(0.46)	6.22(1.23)	0.047	0.999	99.9
o–Cl[a]	9.64(0.18)	11.49(0.19)	–	0.047	0.999	–
m–Cl[a]	10.07(0.69)	12.06(0.71)	–	0.177	0.992	¢
p–Cl[a]	9.86(0.60)	11.78(0.62)	–	0.155	0.993	–
o–NO_2	8.25(0.27)	12.10(0.55)	4.63(1.46)	0.055	0.999	97.5
m–NO_2	9.10(0.31)	16.67(0.63)	12.62(1.69)	0.064	0.999	99.9
p–NO_2	9.62(0.29)	13.72(0.59)	5.03(1.58)	0.060	0.999	99.9
p–SCH_3	9.41(0.31)	13.25(0.62)	4.59(1.66)	0.063	0.999	95.0
p–CN	8.19(0.18)	11.87(0.37)	5.39(0.98)	0.037	0.999	99.9
p–F	8.40(0.22)	11.42(0.44)	3.29(1.19)	0.045	0.999	97.5
p–Br	9.41(0.56)	14.95(1.13)	7.53(3.01)	0.114	0.997	97.5
phenol	6.32(0.28)	10.54(0.56)	6.83(1.51)	0.057	0.998	99.9

[a] In contrast to the remaining phenols *p*–nitrophenol and chlorophenols showed no dependence on β_m.

$$r=0.996,\ sd=0.075 \quad (10)$$

Incorporation of HB acidity obviously improves the quality of the fit. In order to ascertain whether purely statistical considerations warrent the inclusion of a dependence on a second parameter, we used the Ehrenson test[31] to determine confidence level (CL%) that the single regression may be rejected in favor of the double regression. Only when CL% for the second variable are >90% is the multiple parameter correlation statistically justified. The Ehrenson test indicates that the α_m parameter is significant at the 99.5% confidence level. Since the phenols are also quite acidic in HB, it seems necessary to include the HB basicity of the mobile phase in the regression equation. The three parameter equation we obtained is:

$$\begin{aligned} lnk' &= -7.49\,(\pm 6.16) + 7.00\,(\pm 1.00)\,\pi^*_m \\ &\quad + 1.22\,(\pm 4.78)\,\alpha_m - 3.05\,(\pm 3.79)\,\beta_m \\ r&=0.996,\ sd=0.084 \end{aligned} \quad (11)$$

We find there is no improvement in the goodness of the fit and the coefficient for β_m is statistically zero. The Ehrenson test also shows that the third parameter is not significant. For the remaining phenols we observed the same results. The double regression results for all phenols studied are listed in Table 3.

Based on these regression results it seems that the RPLC retention of phenols in methanol–water system is determined by dipolar and type A HB interactions between the solute and the mobile phase. However, the signs of the s'' and b'' coefficients are positive. This is quite opposite to the result obtained from the correlation *vs.* solute properties (eq. 8). Increasing mobile phase dipolarity and HB acidity shouid increase the solubility of phenol in polar and hydrogen bonding mobile phase, thus causing the retention to decrease. However, we may view these results in a different perspective. We have shown in a previous study[27] that the solvophobicity scale (S_p) of Abraham *et al.*[32] for methanol–water mixtures can be described very well by a combination of the dipolarity and HB acidity of the mixture as given below and that the HB basicity of the mixture does not play a role.

$$S_p = -1.44 + 1.22\,\pi^*_m + 0.81\,\alpha_m$$
$$n = 9,\ r = 0.998,\ sd = 0.02$$

On this basis we may say that retention of phenols in methanol–water mobile phases are controlled by the solvophobic forces, which cause solubility of the solute to increase in less polar stationary phase, resulting in increase in retention. The S_p values were determined based on the Gibbs free energies of transfer of inert solutes from water to the second liquid. Thus it is likely that difference in the cavity formation term in the two liquid was already included in the S_p. Retention process in RPLC also involves transfer of the solute between the mobile and stationary phase. Indeed, results of simple regressions of lnk' for phenols *vs.* S_p gave excellent correlations, giving the average correlation coefficient of over 0.99. This is in good agreement with the fact that retention of phenols in RPLC is well correlated with the mobile phase dipolarity and HB acidity. In view of the fact that the S_p values are based on transfer free energies of *inert* solutes, excellent correlations between retention of *polar* and *hydrogen bonding* phenols and S_p are surprising.

While Table 3 contains the entire body of regression data in water–methanol system, it is of interest to highlight the effects of changes in the mobile phase dipolarity and HB acidity on various molecular properties such as substituent or position of the substituent by viewing the data in a different fashion. Coefficients s'' and b'' are all different for phenols with different substituents, as expected from good separation of different phenols in methanol–water system at various compositions. For positional isomers the ratios of b''/s'' are all different and in general greater for meta-isomers than for ortho- and para-isomers. Even though excellent correlations were observed in both regressions of lnk' *vs.* S_p and *vs.* π^*_m and α_m we still think that the regression equation may not be complete without including an explicit cavity term. Thus it seems inappropriate to attempt to rationalize the meaning of the differences in the b''/s'' ratio. It suffices to say at this point that the retention process for phenols in methanol–water system is likely to be controlled by the solvophobic force for a limited composition range examined here.

Acetonitrile– and Tetrahydrofuran–Water System. Regressions of lnk' *vs.* mobile phase properties for acetonitrile (ACN)–water system were performed in a similar manner. In contrast to the methanol system, retention behavior of various phenols was well described with only π^*_m, except three amino-substituted isomers (see Table 4) while in tetrahydrofuran (THF)–water system retention was well correlated with π^*_m and β_m (see Table 5). We do not have a firm explanation for this difference. We think that this difference in correlation behavior between the methanol system and ACN and THF systems is likely to originate due in part to higher HB acidity of methanol mixture than those of ACN and THF mixtures. The smaller HB acidity of the ACN mobile phases render themselves to possess less hydrophobicity and this, in turn, make the dipolarity become a major factor to cause hydrophobic interactions of phenols with the less polar stationary phase to occur. Also note that β_m values for the THF mixtures are generally greater than those for the ACN mixtures. This may provide an explanation to why the β_m dependence of retention for phenols is important in THF–water system. Note in Table 5 that the sign of the a'' coefficient is negative, indicating that increasing the HB basicity of the mobile phase decreases retention of phenols which are acidic in HB. S_p values for ACN and THF mixtures were not available and no regression *vs.* S_p was done.

Conclusion

Under the condition that the modification of the stationary phase due to the change in the amount of the organic cosolvent in the mobile phase is very small and eq. (6) also holds for aqueous mixtures, retention properties of phenols in RPLC are well representated by regression equations *vs.* solvatochromic mobile phase parameters based on LSER. Dependence of retention behavior of mono-substituted phenols studied in this work on the mobile phase properties were varied depending on the type of the organic cosolvent in the mobile phase, *e.g.*, π^*_m and α_m in methanol–water system, but π^*_m and β_m in THF–water system. This may provide an explanation, although in a limited sense, for the change in the elution order of a particular solute when the mobile phases is changed from methanol–water to THF–water, which Scho-

enmakers *et al.*[33] called specific mobile phase effect. Once δ_m values for aqueous mixtures become available the solvatochromic LSER equation (eq. 4) will provide even better understanding of intermolecular interactions affecting retention processes in RPLC than what is presented in the present study.

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