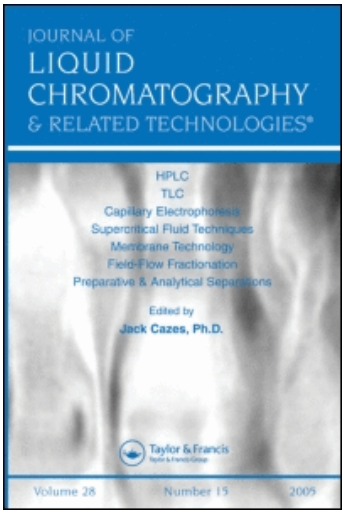

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MODIFIER INFLUENCE ON SELECTIVITY OF REVERSED-PHASE HPLC SYSTEMS

Tadeusz H. Dzido[a]
[a] Department of Inorganic and Analytical Chemistry, Medical Academy, Lublin, Poland

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MODIFIER INFLUENCE ON SELECTIVITY OF REVERSED-PHASE HPLC SYSTEMS

Tadeusz H. Dzido

Department of Inorganic and Analytical Chemistry
Medical Academy
Staszica 6
20-081 Lublin, Poland

ABSTRACT

Correlation of partition constants of nine benzene derivatives in various gas – liquid systems, of which the solutions constitute binary mixtures of water and organic solvents methanol (MeOH), acetonitrile (ACN), tetrahydrofuran (THF), show high values of correlation factor. On the other hand, the correlation of retention, as log k (k – retention coefficient) of the same solutes in high performance reversed phase liquid chromatography (RPHPLC) systems with stationary phase of the C18 type and eluents of similar composition as liquids in the gas – liquid partition systems, reveal much smaller values of correlation factor.

The comparison of these correlation data leads to the inference that interaction of the solute in the stationary phase, especially with sorbed modifier, is responsible for selectivity variation when the modifier is changed in the binary mobile phase of the RPHPLC system. This behavior is additionally confirmed by the retention correlation of phenolic acids for RPHPLC system with the modifiers investigated.

INTRODUCTION

Questions concerned with explanation of retention and selectivity changes of reversed-phase high-performance liquid chromatography systems are not yet

entirely explained in spite of many papers which have been published in professional journals.[1-5] There are some problems under discussion, contrary to the understanding of systems with bare silica and non polar mobile phase, e.g.: is there an adsorption or partition mechanism of retention in RP HPLC? – what is the driven force for retention and selectivity? – what is the structure of the stationary phase, and how stationary phase influences on the separation selectivity?

The main reason for this situation is the involvement of very complex physicochemical structures of this system,[6-8] which is difficult to define. A typical unpolar stationary phase applied in RPHPLC is composed of aliphatic chains attached to the silica surface by covalent bond. The chain length is expressed as a carbon number and usually it is equal to 8 or 18. Properties of such stationary phases are not the same as the appropriate bulk hydrocarbons. There are several main reasons influencing these properties.

Coverage of the stationary phase does not equal the population of the silanol groups on bare silica surface, but it reaches a value of about half of the silanol population on silica surface (approximately 8 ± 1 μmol/m^2 on chromatographic grade silica).[9] Molecular movement of aliphatic chains is restricted to both their terminals. The one chain terminal is attached to the silica surface and the second expelled from the water mobile phase due to hydrophobic effect.[7,10] The effect is especially characteristic in systems with high percentages of water in the mobile phase (> 50% v/v).

Stationary phase is selectively modified by organic components of the mobile phase.[11-15] Sorption of the modifier increases in the order: methanol, acetonitrile, tetrahydrofuran, and depends on the modifier composition.[13,14] In consequence, the thickness of the stationary phase can be varied according to the qualitative and quantitative composition of the eluent. Even modifier distribution in the stationary phase is not homogenous.[16] Water is strongly adsorbed by the non silanized part of the silica surface,[17] and can be solvated, to some extent, by modifier molecules present between aliphatic chain spaces[18]

These effects lead to polarity increase of the stationary phase, which can be more polar than pure isopropanol, depending on the type and concentration of the modifier in the mobile phase.[19] Therefore, composition and volume of the stationary phase (it means surface phase in the light of the short discussion) are so complicated and so do not explain, simply, the retention and selectivity changes in reversed-phase liquid chromatography systems.

The most popular components of the binary mobile phase are methanol, acetonitrile, and tetrahydrofuran. Each solvent possesses different properties which are concerned with molecular interaction between modifier and remaining components of the chromatographic system (water, solutes, hydrocarbon

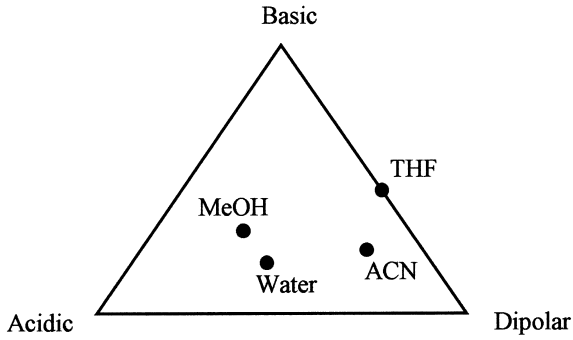

Figure 1. Solvent selectivity triangle based on normalized solvatochromic parameters for three of the most common solvents in RPHPLC.[2,22]

chains, silanol groups). Schematically, the relative share of three types of interactions (dipolar, proton donor, and proton acceptor), based on normalized solvatochromic parameters represented by these modifiers, is demonstrated in Figure 1.[2,20]

Methanol is characterized by its high contribution to interact as proton donor, possessing a strong proton acceptor, and relative high dipolar properties. Acetonitrile has the largest dipole moment but is characterized by weak tendencies to be a proton acceptor and much weaker as a proton donor. In turn, tetrahydrofuran has a stronger proton acceptor property than acetonitrile, but, its ability as a dipolar interaction is lower and shows no ability to be a proton donor. However, tetrahydrofuran molecules have the largest molecular volume of its non polar moiety, which enables an increase in participation in non specific interactions relative to methanol and acetonitrile. It is also reflected in values of index of refraction, which is 1.405 for THF and is distinctly higher than values of methanol (1.327) and of acetonitrile (1.342). Compare, also, solvatochromic parameters of the modifiers in Table 1.[21]

However, it is too simplified an approach to demonstrate the pure modifier's properties in order to explain their influence on retention and selectivity changes in chromatographic reversed-phase systems. The mobile phase properties are also determined by water which is present in almost all RPHPLC systems.[18]

The solvatochromic parameter (π^*) of Kamlet and Taft, describing solvent ability to dipolar/polarizability interaction with solute, increases non-linearly with volume composition of water. Solvent capability, to be as proton donor in

Table 1

Kamlet-Taft Solvatochromic Parameters[21]

Solvent	Dipolarity/ Polarizability, π_1*	Hydrogen Bond Acidity, α_1	Hydrogen Bond Basicity, β_1
Water	1.09	1.17	0.48
Acetonitrile	0.75	0.19	0.31
Methanol	0.60	0.93	0.62
Tetrahydrofuran	0.58	0.00	0.55

hydrogen bond, is described by parameter α, which corresponds to its ability to share an active hydrogen atom with a hydrogen bond acceptor solute, changes the dependence on modifier type in water solution. Small amounts of water added to the modifier (acetonitrile and tetrahydrofuran) contribute to the fast increase of α; afterwards, dependence is flat with further increase of water concentration.

A slight increase of α value is observed at the end of the concentration range. The behavior of water-methanol solution shows an entirely different shape - minimum at the curve of α vs. water percentage. A solvent contribution which is a proton acceptor in hydrogen bond is denoted by β, corresponding to its ability to accept an active hydrogen atom from a hydrogen bond donor solute. Acetonitrile and tetrahydrofuran water solutions show broad and flat maximums depending on β vs. water percentage. Appropriate relationships of water-methanol solutions shows monotonous change, but non-linear shape with water composition.[18]

The properties of solvents (mobile phase) mentioned above characterize their ability to interact molecularly with solutes but, also., between eluent molecules themselves. Energy of these interactions is a key factor in the most popular solvophobic theory for RPHPLC systems elaborated by Horváth et al. in the second half of the seventies.[22,23] According to the theory, an insertion of the solute molecule into the mobile phase is concerned with a cavity formation for this molecule. The process is usually energy-consuming; energy is required to break up solvent structure to create a cavity for the solute molecule. This energy is partly compensated by interaction of solute molecules with surrounding solvent molecules in common reversed-phase systems. In solvophobic theory the surface tension is the key factor which is applied to characterize an ability of the mobile phase solution for the cavity formation. Other parameters used for describing molecular interaction of the eluent are e.g., solubility para-

meter of Hildebrandt[24] or solvophobic scale of Abraham et al.[25] However, the surface tension and the Abraham's solvophobic parameter do not show good correlation.

As it is well known, water shows the strongest cohesive energy density.[3,24] Its value is distinctly higher than remaining solvents. Therefore, other solute molecules, especially non polar, are expelled from the water mobile phase. Tendency for this effect grows according to the increase of molecular volume of the solute. It is expressed by linear relationships log k vs. carbon number in homologous series.[26] However, solutes with different functional groups (e.g. benzene derivatives) do not show good correlation between retention (log k) and molecular volume of the solute.

The discussion above indicates that reversed-phase chromatographic systems are highly complicated. The properties of the mobile phase change nonlinearly with the quantitative composition of the mobile phase. Distinct changes are observed when qualitative composition of the eluent varies. It refers to the stationary phase as well. The solvation interactions between the components of the chromatographic systems and association interactions, especially hydrogen bond formation among molecules of one component - water, which is present practically in all RPHPLC systems,[27] plays a very important role in the explanation of these effects.

EXPERIMENTAL

The data of gas-liquid partition constant of the solutes investigated (acetophenone, anisole, benzaldehyde, benzene, benzonitrile, chlorobenzene, nitrobenzene, phenol, toluene) were taken from the paper of Slaats et al.[28] The values of retention coefficient of the solutes investigated, were taken from the paper of Tanaka et al.[29] The retention coefficient values of phenolic acids were evaluated from the paper submitted for publication.[30]

RESULTS AND DISCUSSION

It is well documented that the modifier change in the eluent strongly influences the selectivity, especially, of polar solutes in RPHPLC systems.[29,31-33] Origin of the effect can take place in molecular interaction of the solute and components of the mobile and stationary phase.[2,34-40] But the question arises, which phase (mobile or stationary), and to what extent, is involved in selectivity changes in the case of modifier variation in the eluent? Then, the answer cannot be, at first, unequivocal. It seems to be obvious in the light of the discussion above, that the change of the modifier in the binary water mobile phase should lead to the variation of the selectivity separation, especially, of polar solutes.

The experimental data confirm this expectation[29,31-35,41] because replacement of a modifier with another, one often causes dramatic changes of retention sequence of the solutes, especially, aromatic compounds with different polar groups. Is there a source of the effect in the molecular interaction in the mobile phase? It seems, that, the answer to the question would be intuitively positive if considering the solvent properties in the light of the discussion above.

However the conviction, that molecular interactions in the mobile phase alone play the key role in selectivity, can be obtained if influence of the stationary phase would be eliminated in partition of the solute between two phases. This requirement can be obtained in the gas-liquid partition system in which liquid is the water organic modifier (methanol, acetonitrile, tetrahydrofuran) solution.

Standard free energy, $\Delta G°$, concerned with transport of the solute, *i*, from the gas phase, *g*, to the liquid phase, *cn*, is expressed as:

$$\Delta G°_{i,(g/c1)} = -RT \ln K_{i,(g/c1)} \quad (1)$$

$$\Delta G°_{i,(g/c2)} = -RT \ln K_{i,(g/c2)} \quad (2)$$

where *K* is the equilibrium partition constant of the solute *i* between two phases gas and liquid *c1* or *c2*. Molecular interaction in the liquid phase and entropy element is the driven force for partition of the solute in gas – liquid system if interaction in the gas phase is omitted.

After subtraction the equation (1) from (2) the correlation equation is obtained:

$$\ln K_{i,(g/c2)} = \ln K_{i,(g/c1)} + (\Delta G°_{i,(g/c1)} - \Delta G°_{i,(g/c2)}) / RT \quad (3)$$

If there is the same or similar partition mechanism in the systems correlated, including interaction of the types: dipolar, inductive, proton donor, proton acceptor, and dispersion between all components of the systems, then the high correlation of the partition constants of two gas-liquid systems should be expected.

Taking into account the discussion above about various abilities of the modifiers become involved in molecular interactions, it seems that the correlation between partition constants of the solutes in the gas-liquid systems should not show high values of correlation factors. However, it is not confirmed by experimental data. The partition constants of the benzene derivatives in the gas-liquid (binary water solutions of 48.4% methanol, 29.7% acetonitrile, 29.7% tetrahydrofuran) systems are correlated in Figure 2, and as equations 4 - 6, respectively, for the systems 48.4% MeOH vs. 29.7% ACN, 29.7% THF vs.

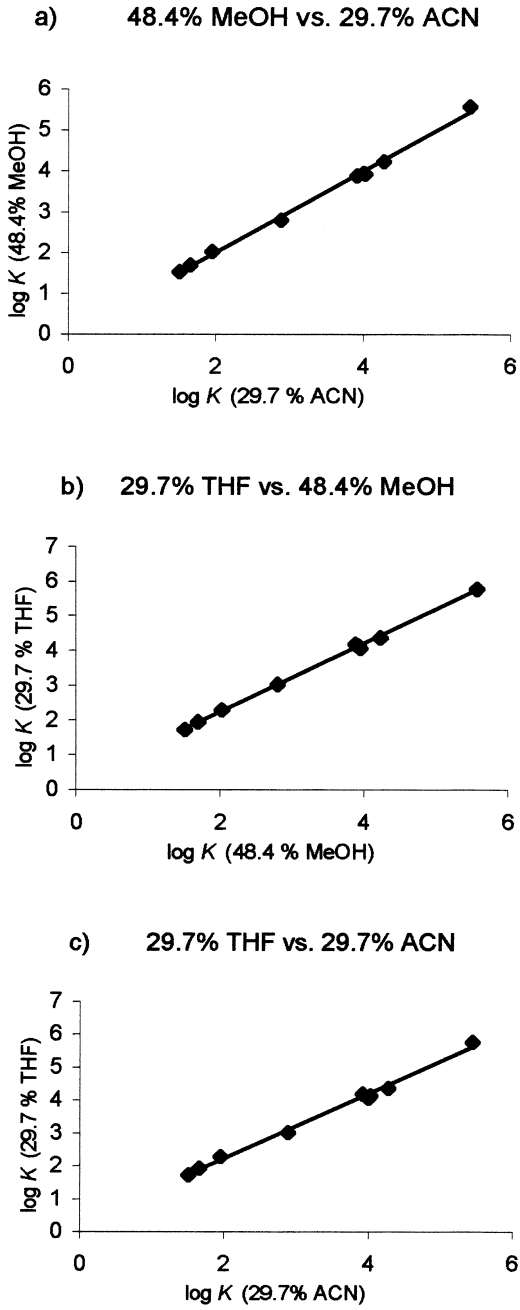

Figure 2. Correlation of the gas-liquid partition constant (log *K*), of some benzene derivatives for the liquid systems: a) - 48.4% methanol vs. 29.7% acetonitrile, b) - 29.7% tetrahydrofuran vs. 48.4% methanol, c) - 29.7% tetrahydrofuran vs. 29.7% acetonitrile.

48.4% MeOH, and 29.7% THF vs. 29.7% ACN. All three pairs of the correlated systems show high values of correlation factor. Its values are greater than 0.99, and the slopes of the plots are very close to 1.0, in spite of the various abilities of the solutes' tendency to undergo molecular interactions (compare also solute solvation parameters in Table 2)[42]

$$\log K_{g/48.4\,\%\,MeOH} = 0.9971 \log K_{g/29.7\,\%\,ACN} + 0.0037 \quad R^2 = 0.9968 \qquad (4)$$

$$\log K_{g/29.7\,\%\,THF} = 0.9857 \log K_{g/48.4\,\%\,MeOH} + 0.2484 \quad R^2 = 0.9983 \qquad (5)$$

$$\log K_{g/29.7\,\%\,THF} = 0.9823 \log K_{g/29.7\,\%\,ACN} + 0.2538 \quad R^2 = 0.9940 \qquad (6)$$

The correlation equations of gas-liquid partition constants for higher concentration of the modifiers in the water solutions, than these demonstrated in Figure 2, also show large values of correlation factor (see the correlation equations 7-9, respectively, for the liquid systems 67.5% MeOH vs. 49.1% ACN, 49.0% THF vs. 67.5% MeOH, and 49.0% THF vs. 49.1% ACN), and their slopes also reach values close to 1.0.

Table 2

Solute Descriptors[42]

Nr.	Solute	Dipolarity/ Polarizability, π_2^{*H}	Hydrogen Bond Acidity, $\Sigma_{\alpha 2}^{H}$	Hydrogen Bond Basicity, $\Sigma_{\beta 2}^{H}$
1	Acetophenone	1.01	0	0.48
2	Anizole	0.75	0	0.29
3	Benzaldehyde	1.00	0	0.39
4	Benzene	0.52	0	0.14
5	Bezonitryle	1.11	0	0.33
6	Chorobenzene	0.65	0	0.07
7	Nitrobenzene	1.11	0	0.28
8	Phenol	0.89	0,60	0.30
9	Toluene	0.52	0	0.14

$$\log K_{g/67.5\%MeOH} = 0.9648 \log K_{g/49.1\%ACN} + 0.0033 \quad R^2 = 0.9978 \qquad (7)$$

$$\log K_{g/49.0\%THF} = 1.0188 \log K_{g/67.5\%MeOH} + 0.3768 \quad R^2 = 0.9910 \qquad (8)$$

$$\log K_{g/49.0\%THF} = 0.9832 \log K_{g/49.1\%ACN} + 0.3725 \quad R^2 = 0.9893 \qquad (9)$$

These relationships indicate that partition mechanism of the solutes in the gas-liquid systems is very similar. Participation of modifier molecules in comparison to water molecules, in competition for interaction with solute molecules, plays a minor role. Additionally, it should be mentioned that high concentrations of the modifier means relatively high molar fractions of water (67.5% v/v of methanol corresponding to 0.51 mole fraction of water; 49% v/v of tetrahydrofuran is 0.82 mole fraction of water and 49% v/v of acetonitrile-0.75 mole fraction of water). This implies that change of modifier in the liquid phase has minor influence on partition selectivity. But influence of water on the process is dominant.

The results presented above have repercussion for the reversed-phase liquid chromatography systems: the binary mobile phase alone does not influence, or this influence is minor, on selectivity variation if modifier is changed in the eluent (by leaving approximately the same value of elution strength and relatively high concentration of water). The other papers partly confirm this conclusion because binary mobile phases composed of methanol or acetonitrile with water concentration higher than 50% show similar abilities as dipolar interaction and hydrogen bond formation.[43-45]

However, the correlation of retention, log k, of the same solutes for the reversed-phase systems with the stationary phase of the C18 type, and the mobile phases of similar composition as liquid applied in the gas-liquid partition systems, results in quite distinct dispersion of points. Figure 3 shows these correlation plots for the pairs of eluent systems: a) 50% MeOH vs. 30% ACN, b) 25% THF vs. 50% MeOH, and c) 25% THF vs. 30% ACN.

This effect is additionally confirmed by smaller values of correlation factor of the equations 10 - 12 for these systems than for the partition systems.

$$\log k_{50\%MeOH} = 1.0534 \log k_{30\%ACN} + 0.3122 \qquad R^2 = 0.9709 \qquad (10)$$

$$\log k_{25\%THF} = 1.0187 \log k_{g/50\%MeOH} + 0.3963 \qquad R^2 = 0.8799 \qquad (11)$$

$$\log k_{25\%THF} = 0.9320 \log k_{30\%ACN} + 0.1192 \qquad R^2 = 0.8416 \qquad (12)$$

The comparison of both kinds of the results, of the partition gas-liquid and the RPHPLC systems, can be presumed for the following inference: molecular interactions of the solute with components of the stationary phase are basic rea-

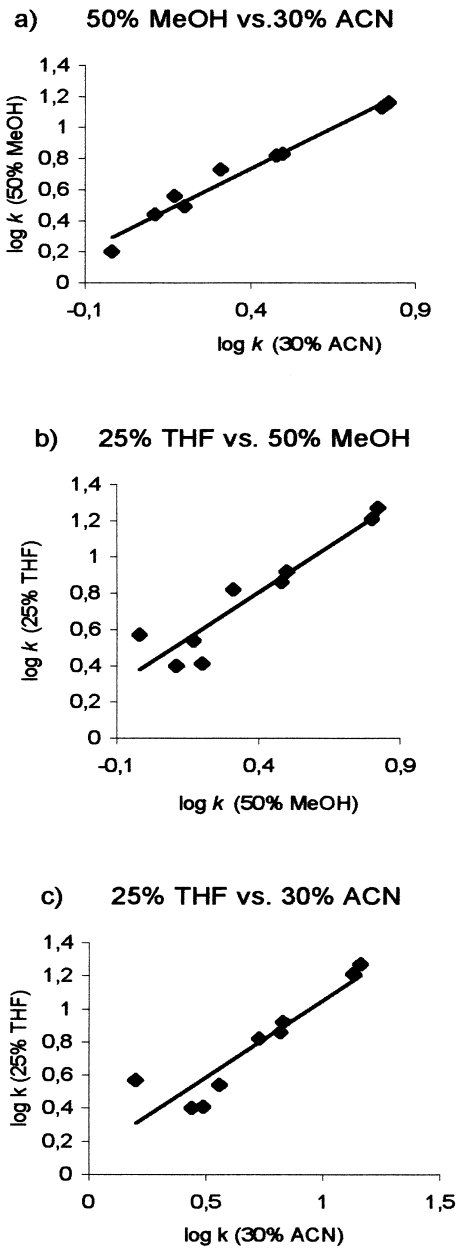

Figure 3. Correlation of the retention coefficient (log *k*) of some benzene derivatives (acetophenone, anisole, benzaldehyde, benzene, benzonitrile, chlorobenzene, nitrobenzene, phenol, toluene) for RPHPLC systems with binary water eluents: a) - 50.0% methanol vs. 30.0% acetonitrile, b) - 25.0% tetrahydrofuran vs. 50.0% methanol, c) - 25.0% tetrahydrofuran vs. 30.0% acetonitrile.

sons for selectivity variation of reversed-phase liquid chromatography systems of the C18 type if the modifier of the mobile phase is changed. The qualitative and quantitative composition of the stationary phase is far more complicated in the chromatographic system than in its pure state, as was discussed above. It can be expressed that stationary phase with the binary water eluent forms systems at least with four components, which is comprised of hydrocarbon chains, modifier molecules, silanol groups, and water.

The composition of hydrocarbon chains is constant with silanols and sorbed water on it as well. In turn, the presence of water in the stationary phase in the space between hydrocarbon chains is restricted.[13-15] Thence, molecular interactions of the solute, especially with polar groups, and the modifier do not meet strong competition of water molecules as it takes place in the mobile phase. Therefore, the modifier type and its interaction with solutes in the stationary phase plays a crucial role for selectivity changes of benzene derivatives.

It should be mentioned that modifier concentration in the stationary phase can be varied depending upon its type and concentration in the mobile phase, which can additionally complicate properties of the chromatographic system with regard to the selectivity.

The results for phenolic acids seems to confirm the modifier influence on selectivity changes, presented in the paper. In Figure 4, the retention of phenolic acids[30] is correlated for systems consisting of the stationary phase of the C18 type and binary eluents with the modifiers investigated (25% methanol, 12% acetonitrile, 20% tetrahydrofuran). It is not possible to compare partition data of the solutes in gas-liquid partition systems for the discussion due to very low volatility of the solutes. But, it should be underlined that higher concentration of water in the mobile phase leads to a much stronger decrease of participation of molecular interactions between modifier and solute in the eluent phase than in that mobile phase of the systems correlated above (with lower concentration of water).

So, such mobile phases should be featured by further lowering of the influence on selectivity alteration by the modifier change in comparison to the mobile phases with smaller concentration of water. As it is demonstrated in Figure 4a, the log k values of eleven phenolic acids show very good correlations for the methanol and acetonitrile systems. It is reasonable because both modifiers show relatively low sorption on the stationary phase from solutions of such small concentration. However, tetrahydrofuran, regarding its stronger hydrophobicity and ability to dispersion interaction relative to methanol and acetonitrile, is more strongly sorbed on/in the stationary phase.[13,14] This is reflected by substantial dispersion of points in Figure 4b and 4c, which refer, respectively, to 20% THF vs. 25% MeOH and 20% THF vs. 12% ACN systems.

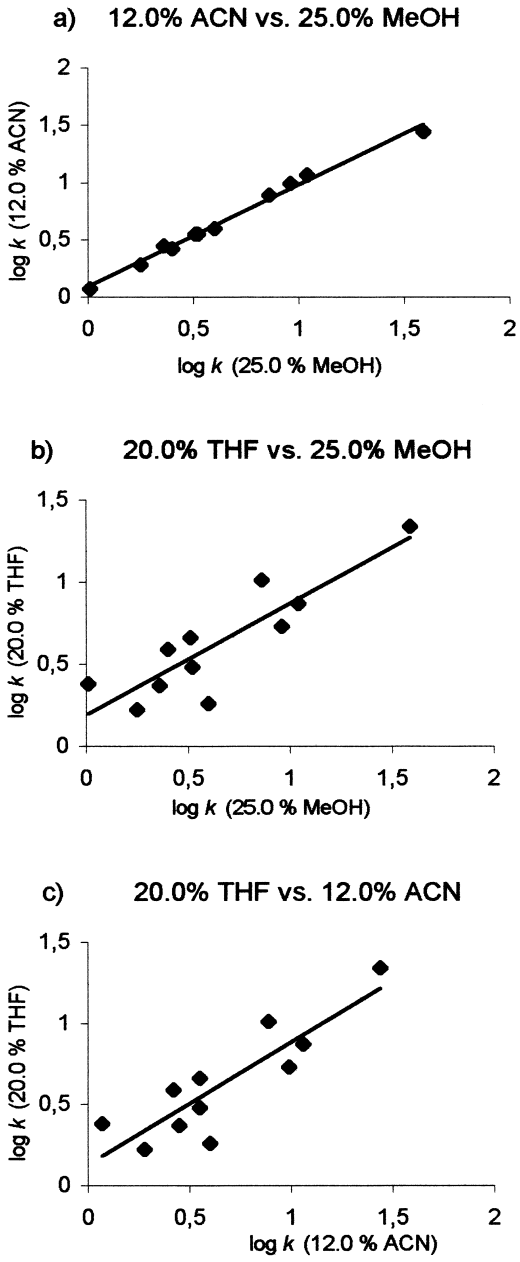

Figure 4. Correlation of the retention coefficient (log *k*) of some phenolic acids (caffeic, chlorogenic, 3-coumaric, 4-coumaric, ferulic, hydrocaffeic, hydroxybenzoic, protocatechuic, rosmarinic, syringic, vanillic) for RP HPLC systems with binary water eluents: a) - 12.0% acetonitrile vs. 25.0% methanol, b) - 20.0% tetrahydrofuran vs. 25.0% methanol, c) - 20.0% tetrahydrofuran vs. 12.0% acetonitrile.

An important role for explanation of such behavior seems to involve the ability of THF molecules to undergo specific interactions as hydrogen acceptors. Additionally, the decrease of the elution strength of the tetrahydrofuran system relative to the methanol and acetonitrile systems, which can be observed in Figure 4 (similar average retention of the solutes is demonstrated in the three types of the systems correlated but THF concentration in the mobile phase is higher than ACN and slightly lower than MeOH) in comparison to the data in Figure 3, can be also interpreted in terms of higher activity of the stationary phase caused by sorption of tetrahydrofuran.

CONCLUSIONS

Relative retention changes of polar solutes in reversed phase liquid chromatography systems with binary eluents consisting of various modifiers, e.g., methanol, acetonitrile, or tetrahydrofuran, are mainly caused by molecular interactions between the solute and the modifier in the stationary phase.

The differences of the retention between two binary eluent systems seem to be very interesting for finding the separation conditions in ternary solvent systems with regard to a composition of the modifiers in the stationary phase.

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