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The Application of the Extended Thermodynamic Approach to Describe the Effect of Counterions, Both of Chaotropic Agents and Ionic Strength Modifiers, on the Retention Behavior of Protonated Basic Analytes in Chaotropic Chromatography

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Abstract

In this study, the extended thermodynamic approach was used to quantitatively explain the effect of counterions, both of chaotropic agents and ionic strength modifiers, in variable (*vI*) and constant ionic strength (*cI*) systems on the retention behavior of 23 fully protonated basic analytes. Nine series of experiments (at three pH values for $NaPF_6$, KPF_6 and NH_4PF_6) with *vI* and nine series of experiments (at three pH values for $NaPF_6$, KPF_6 and NH_4PF_6) with ionic strength kept constant with NaCl, KCl and NH_4Cl were performed. The experimentally determined retention factors were modeled using the extended thermodynamic approach and the processes occurring in the stationary phase and in the mobile phase and their influence on retention in the investigated chaotropic chromatography systems were rationalized. In both *vI* and *cI* systems, ion pair formation in the stationary phase proved to be dominant over ion pair formation in the mobile phase. In the KPF_6_*vI* systems, these interactions with the stationary phase were even more pronounced than in the other systems. Although both K^+ and NH_4^+ are chaotropic in nature, the formation of ion pairs in the stationary phase was favored by the presence of $NH4^+$ only at its rather high concentrations as in *cI* systems.

Key words: extended thermodynamic approach, chaotropic chromatography, retention behaviour, effect of counterions

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Introduction

Chaotropic agents are a type of ion-interaction agents (IIAs) that undergo reversible interactions with the stationary phase and only affect the chromatographic behavior of protonated basic analytes. In this type of ion interaction chromatography, also known as chaotropic chromatography, the surface of the stationary phase is converted into a pseudo-ion exchange stationary phase with the addition of chaotropic ions to the mobile phase and their adsorption on the hydrophobic surface of the stationary phase (1, 2). In this way, ionic interactions can be established with the charged analyte both in the mobile phase and with the ions adsorbed on the stationary phase. The mechanism of analyte retention in these systems is very complex and chromatographic processes can be represented by a series of equilibria and their stoichiometric constants. Understanding, explaining and predicting the retention behavior of analytes is a prerequisite for optimizing chromatographic separations and simplifying the development of suitable chromatographic methods (1, 2). Chromatographic retention models can be empirical or theoretical and are a mathematical representation of the dependence of the retention behavior of analytes on the influence of the components of the chromatographic system. Empirical models do not require a theoretical basis to describe retention data, while theoretical models apply known physicochemical principles and translate raw data into knowledge of fundamental importance (1).

Cecchi et al. (3–5) developed an extended thermodynamic model that enables the theoretical modeling of retention behavior in chaotropic chromatography. This model considers the retention of analytes from both a stoichiometric and a thermodynamic point of view. This approach takes into account both the thermodynamic constants of ion pair formation and the importance of the development of an electric double layer on the stationary phase. A very important feature of the extended thermodynamic retention model is its ability to quantitatively predict the behavior of charged, multiply charged, neutral and zwitterionic solutes in the presence of chaotropes (2) and also to quantitatively explain the influences of the concentration of organic modifiers and ionic strength. The model was originally developed for chromatographic systems with ion pairs, but its application has also been confirmed in chaotropic chromatography systems (1–5).

The extended thermodynamic approach was criticized by Stahlberg (6) on the grounds that it was “too complicated for practical application”, there is a large number of adjustable constants and finally the author argued that there is no “single set of experimental retention data that can be analyzed with the model”. Contrary to this opinion, our group’s results suggest that the extended thermodynamic approach is readily applicable and can provide further useful insights into key retention phenomena (7). Čolović et al. (8) applied the extended thermodynamic model to investigate the pH-dependent retention behavior of 13 fully protonated basic solutes in chaotropic chromatography and to distinguish it from the effects of ionic strength. It is known that the value of the surface potential (Ψ^0) can also be affected by the nature of the chaotropic counterion (cation), as adsorbophilic counterions can reduce the net surface charge (2, 3).

In line with this and with the conclusions of the study by Čolović et al. (8), there was a need to further investigate the effects of the type and nature of counterions, both from chaotropic agents and ionic strength modifiers, on the retention behavior of basic solutes in chaotropic chromatography. In our recent study (9), we investigated the effect of different counterions (K^+, Na^+ and NH_4^+ originating both from chaotropic salt and ionic strength modifier) and molecular structure on the retention behavior of protonated basic solutes in chaotropic chromatography. The contribution of analyte interactions with the electrical double layer, ion pairing at the stationary phase and ion pairing in the mobile phase were quantified with the application of empirical model developed by Čolović et al. (8). On the other hand, the aim of the present study was to apply an extended thermodynamic approach developed by Cecchi et al. (3–5) to rationalize the processes occurring in both the stationary phase and the mobile phase and their influence on the retention of analytes on the stationary phase in the studied chaotropic chromatography systems.

Experimental

In our study, nine sets of experiments (at three pH values for three studied chaotropic salts) with varying ionic strength (*vI*) and nine sets of experiments (at three pH values for three studied chaotropic salts) with constant ionic strength (*cI*) were performed. Chemicals, solutions and chromatographic conditions were the same as presented in reference (9).

Retention Modeling with the Extended Thermodynamic Model

The explanation of the basic principles and equilibria underlying the extended thermodynamic model in chaotropic chromatography should begin with the adsorption of the chaotropic agent on the stationary phase. The adsorption profile was determined using the frontal analysis method, and for the present research, determination of the adsorption isotherms of $NaPF_6$, KPF_6 and NH_4PF_6 salts is described in detail in reference (9). The relationship between the amount of the chaotropic agent adsorbed on the surface of the stationary phase and its concentration in the mobile phase can be described by the Freundlich adsorption isotherm (3):

$$[LH] = a[H]^b \qquad [1]$$

where *a* and *b* are experimentally determined constants, $[LH]$ is the amount of chaotropic agent adsorbed on the stationary phase (μmol/m^2), while $[H]$ represents chaotropic agent concentration in the mobile phase (mM). The results for the Freundlich constants (a, b) with the coefficients of determination (R^2) for the selected chaotropic salts are listed in Table S1 in reference (9).

The Freundlich isotherm makes it possible to calculate the electrostatic potential difference Ψ^o that developes between the surface of the stationary phase and the mobile phase. The Guy-Chapman expression (10) for calculating the electrostatic potential has the following form:

$$\Psi^{\circ} = \frac{2RT}{F} ln\left\{\frac{[LH]\cdot|z_H|F}{(8\varepsilon_0\varepsilon_r RT\sum_i c_{0i})^{0.5}} + \left[\frac{([LH]\cdot z_H F)^2}{8\varepsilon_0\varepsilon_r RT\sum_i c_{0i}} + 1\right]^{0.5}\right\} \qquad [2]$$

where z_H is the charge of chaotropic agent, $[LH]$ is the surface concentration of chaotropic agent, ε_0 is the electrical permittivity of the vacuum, ε_r is the dielectric constant of the mobile phase, R and F are the gas and Faraday constants, respectively; T is the absolute temperature and Σc_{0i} is the mobile phase concentration (mM) of electrolyte ions. The above equation [2] shows the dependence of Ψ^0 (mV) on the $[LH]$ (μmol/m^2) and the electrolyte concentration in the mobile phase.

The dependence of the retention of the analyte on the concentration of the chaotropic agent can be represented by the following equation [3] (3):

$$k = \Phi[L]_{\mathrm{T}} \frac{K_{LE}(\gamma_L\gamma_E/\gamma_{LE})exp\left(\frac{-z_E F\Psi^0}{RT}\right)+K_{EHL}(\gamma_E\gamma_H\gamma_L/\gamma_{EHL})[H]}{(1+K_{EH}(\gamma_E\gamma_H/\gamma_{EH})[H](1+K_{LH}(\gamma_L\gamma_H/\gamma_{LH})exp\left(\frac{-z_E F\Psi^0}{RT}\right)[H])} \qquad [3]$$

where K_{LE}, K_{LH}, K_{EH}, and K_{EHL} are thermodynamic equilibrium constants for adsorption of the eluite E onto the stationary phase site L, the adsorption of chaotrope H onto L, the ion pair formation between E and H in the mobile phase (EH), the ion pairing interaction of E with the stationary phase (EHL), respectively and γ represents the activity coefficient for each species.

When the Guy-Chapman expression for the potential and the Freundlich equation for the adsorption isotherm are substituted into equation [3], the final expression for the extended thermodynamic model is obtained:

$$k = \frac{c_1\left\{(a[H]^b f+\left[(a[H]^b f)^2+1\right]^{0.5}\right\}^{\pm 2|z_E|}+c_2[H]}{(1+c_3[H])\left\{1+c_4[H]\left\{a[H]^b f+\left[(a[H]^b f)^2+1\right]^{0.5}\right\}^{(-2|z_H|)}\right\}} \qquad [4]$$

where a and b are constants that are related to the Freundlich isotherm; $[H]$ is the chaotropic salt concentration in the mobile phase; z_E and z_H are the charges of the analyte and chaotropic agent, respectively; and c_1–c_4 represent fitting parameters with clear physical meanings (3, 4). The constant f (m^2/mol) can be estimated from experimental conditions by the following equation [5]:

$$f = \frac{|z_H|F}{(8\varepsilon_0\varepsilon_r RT\sum_i c_{0i})^{0.5}} \qquad [5]$$

where z_H is the charge of the chaotropic ion, ε_0 is the electric permittivity of vacuum, ε_r is the relative permittivity of the mobile phase, and Σc_{0i} is the mobile phase concentration of electrolyte ions.

Parameter c_1 stands for the retention of the analyte without the addition of a chaotropic agent and in our study, it was determined experimentally and not adjusted. Parameter c_2 represents the thermodynamic equilibrium constant of ion pair formation at the stationary phase and parameter c_3 represents the thermodynamic equilibrium constant of ion pair formation in the mobile phase. Parameter c_4 represents the equilibrium constant for the adsorption of the chaotropic agent on the stationary phase and can be considered insignificant and excluded from further modeling when weakly adsorbophilic chaotropic agents are involved (3, 11).

Statistical Analysis

Extended thermodynamic model fittings were performed using STATISTICA (StatSoft Inc, Tulsa, OK, USA) (12). The coefficients were omitted if it was unreasonable to include them (e.g. a negative estimate, a correlation coefficient increased by omission) and consequently the influence of that particular fitting parameter was considered negligible in the investigated chromatographic systems (3).

Results and Discussion

When considering retention processes in chaotropic chromatography, the property of chaotropic agents to adsorb on the surface of the stationary phase and form an electrical double layer should also be taken into account. It is assumed that chaotropic ions (anions) are much more adsorbophilic than their counter ions (cations) and that a negatively charged surface is formed when they adsorb on the stationary phase. The charged stationary phase then attracts the counter ions and an electrical double layer is formed. The analytes have the possibility to interact with the double layer on the surface of the stationary phase, either by ion exchange and/or by adsorption on the surface due to the different electrostatic potential (1). Obviously, the retention behavior of fully protonated basic solutes in chaotropic chromatography can be influenced not only by the chaotropic anion, but also by its counterion. Therefore, we wanted to investigate the effects of the type and nature of the counterion of both the chaotropic agent and the ionic strength modifier on the retention behavior.

For this purpose, three different cations (Na^+, K^+ and NH_4^+) were included in the study, all in the form of a salt with hexafluorophosphate (PF_6^-), which has the highest chaotropicity and the greatest influence on the retention of protonated basic analytes. The effect of the individual cations was investigated in a series of experiments with varying ionic strength (*vI*) i.e. by varying the concentration of the chaotropic salt and the pH value of the mobile phase. Additionally, the above experiments were repeated in the same order, but with constant ionic strength (*cI*). Namely, mobile phases with different concentrations of the chaotropic salt were prepared, the pH of the mobile phase was adjusted and finally NaCl, KCl and NH_4Cl were used to keep the *I* constant when $NaPF_6$, KPF_6 and NH_4PF_6 were used as the mobile phase additives, respectively. For a comprehensive study that effectively and unambiguously describes the retention behavior of 23 investigated protonated basic solutes, the extended thermodynamic approach, proposed by Cecchi et al. (3), was implemented. This model is the most comprehensive theoretical model suitable for describing retention in chaotropic chromatography systems. It was therefore chosen to rationalize the processes that occur in both the stationary phase and the mobile phase and their influence on the retention of analytes on the stationary phase in both studied systems. The experimentally determined values of the retention factors were modeled by an extended thermodynamic model, which is given in equation [4].

Parameters c_2 and c_3 were estimated based on data collected for seven different concentrations of $NaPF_6$, KPF_6 or NH_4PF_6 at each pH value. The assessment of all parameters had satisfactory R^2 values (≥ 0.95). In the present study, we have a set of 13 solutes that are 100% in the form of monocations at all pH values studied (sertraline hydrochloride, fluoxetine hydrochloride, mianserin hydrochloride, tramadol hydrochloride, duloxetine hydrochloride, fenoterol, aripiprazole hemifumarate, verapamil hydrochloride, amitriptyline hydrochloride, ropinirole hydrochloride, clopiramine hydrochloride, thioridazine hydrochloride and maprotiline hydrochloride given in Figure S1 in reference (9)), and a set of 10 solutes whose dominant ionization state is different at the pH values studied (dabigatran etexilate mesylate, risperidone hydrochloride, pheniramine maleate, chlorpheniramine maleate, fluvoxamine maleate, desloratadine hydrochloride, loratadine, cinnarizine, cetirizine hydrochloride, lamotrigine given in Table S2 and Figure S2 in reference (9)). The experimentally determined values of the retention factors for both sets were modeled by an extended thermodynamic model in Cecchi and Pucciarelli (3) and presented in this paper with equation [4]. The model adapted for zwitterions (13) or the one adapted for solutes in dicationic form (14) were not used because we mainly had the combination of ionization states. For example, for cetirizine hydrochloride at pH 2 we had 41.05% monocation 56.29% dication and 2.66% zwitterion. The ionization state in the second set of analytes was 100% monocation on several occasions – risperidone hydrochloride at pH 4.00, desloratadine hydrochloride at pH 2.00 and lamotrigine at pH 2.00 and 3.00 (see Table S2 in reference (9)). Additionally, in (4), the authors assessed the wide applicability of the extended thermodynamic approach using classical cationic and anionic analytes, but also a zwitterionic ones.

An increase in the values of parameters c_2 and c_3 with the increase in the pH of the mobile phase in *vI* was observed. Since parameter c_2 describes the ion pairing on the stationary phase, an increase in the value of this parameter is expected at higher pH values of the mobile phase, which favors the adsorption of PF_6^- ions on the stationary phase surface. Higher values of parameter c_2 indicated a stronger ion pairing between the chaotropic agent and the positively charged basic analyte on the stationary phase surface, which leads to a longer retention of the analyte at higher pH values of the mobile phase. Parameter c_3 changes with increasing pH of the mobile phase in the same direction as parameter c_2. However, the c_3 values were drastically lower compared to parameter c_2 under the same experimental conditions. Therefore, Figure 1 only shows the values of c_2 for "chaotrope-sensitive" solutes (solutes with a change in retention factor $k_{50\ \mathrm{mM}} - k_{1\ \mathrm{mM}} > 5$) in both tested systems.

Since the [LH] has a direct influence on retention modeling using equation [4], the information on the variation of [LH] as a function of [H] in *vI* and *cI* systems is shown in Figure 2.

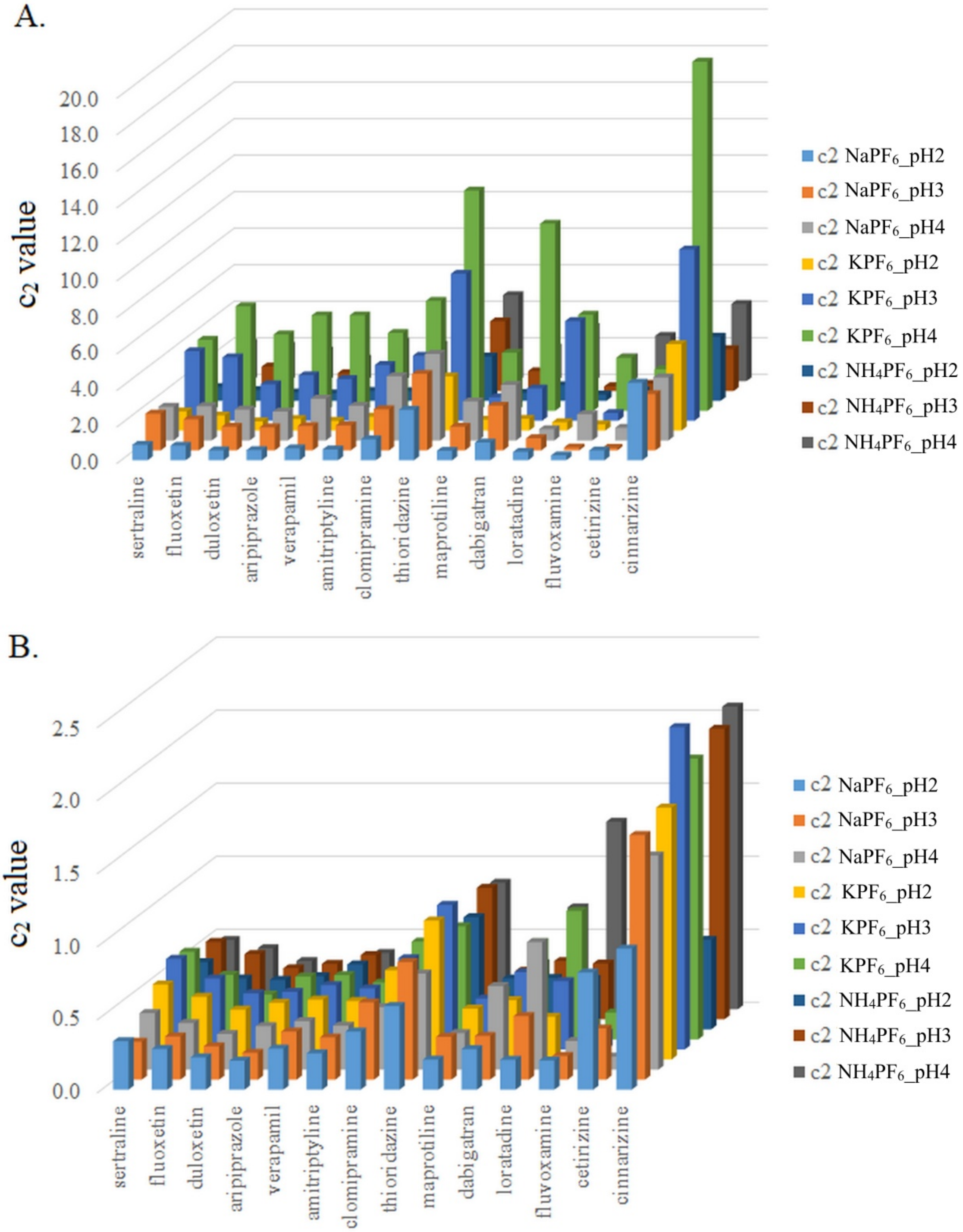

Figure 1. **Coefficient c_2 values vs. mobile phase pH for the “chaotrope-sensitive” solutes in A. *vI* systems and B. *cI* systems**

Slika 1. **Vrednosti c_2 koeficijenata vs. pH vrednost mobilne faze za „haotrop-senzitivne” analite u A. *vI* sistemima i B. *cI* sistemima**

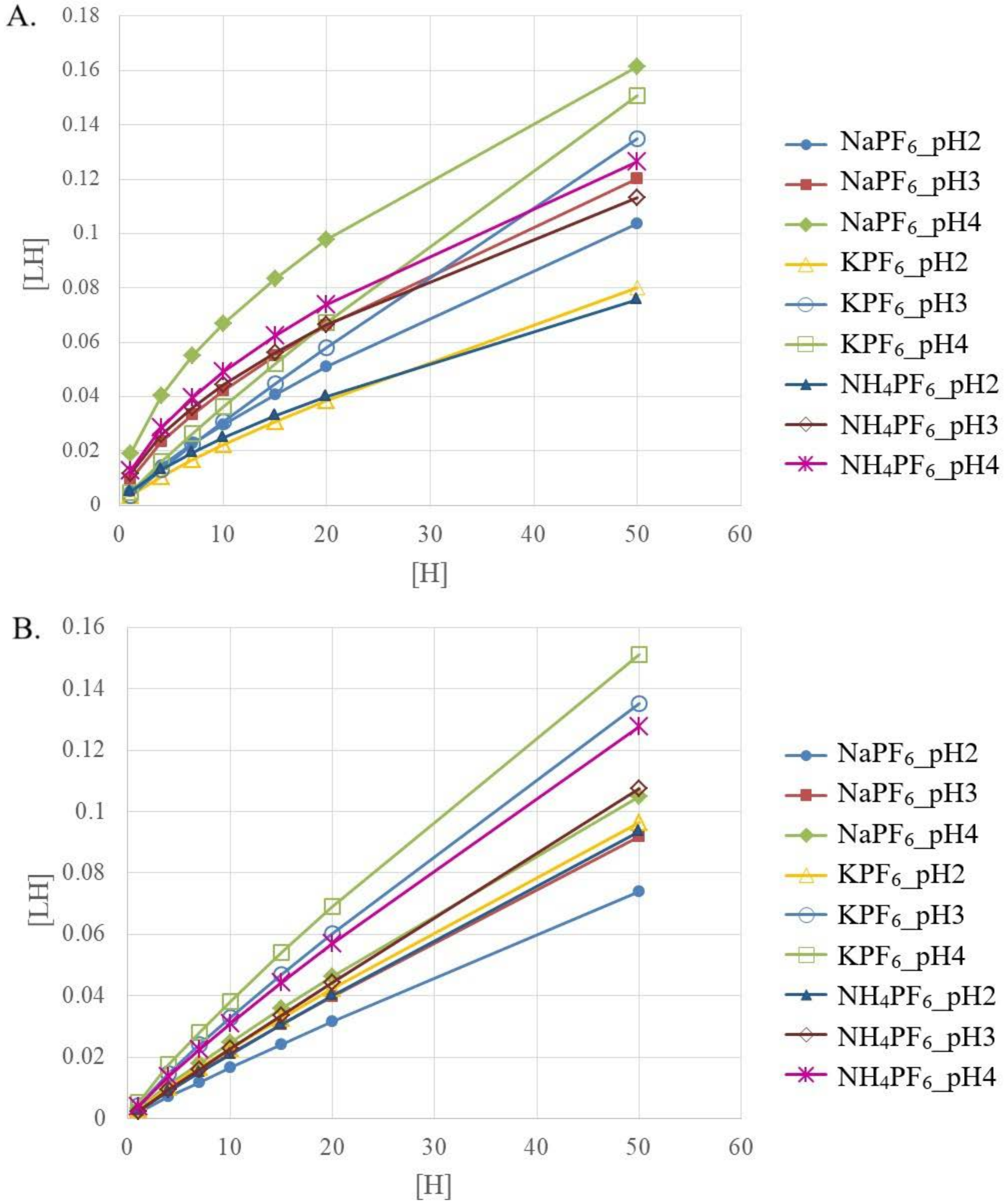

Figure 2. **[LH] obtained at 1 to 50 mM of NaPF$_6$, KPF$_6$ and NH$_4$PF$_6$ in A. *vI* systems and B. *cI* systems**

Slika 2. **[LH] određene za koncentraciju od 1 do 50 mM NaPF$_6$, KPF$_6$ i NH$_4$PF$_6$ u A. *vI* sistemima i B. *cI* sistemima**

The calculated values of c_2 were not completely in agreement with the [LH], as all "chaotrope-sensitive" analytes showed significantly higher values of c_2 when KPF_6 was applied under *vI* for the whole pH range (Figure 1A). The most striking differences were at pH 3 and 4, as the values of c_2 were significantly higher for the KPF_6 *vI* system compared to c_2 of $NaPF_6$ and NH_4PF_6 *vI* system. However, the most controversial results were obtained for the $NaPF_6$ *vI* system, as the calculated c_2 values did not match the calculated [LH] values (Figure 2A), which should actually give the highest c_2 values. The estimated c_2 values, which were in full agreement with the calculated [LH], were obtained when NH_4PF_6 was applied under *vI* for the entire pH range. For NH_4PF_6_*vI* systems, the c_2 values were the lowest compared to the $NaPF_6$_*vI* and KPF_6_*vI* systems and were consistent with the observed [LH] values. The results of this study indicated that the nature of the counter ion (cation) of the chaotropic agent is an important factor in the retention mechanisms. The effect of the counter ions is expressed not only by their influence on the total surface charge of the stationary phase, but also by the structure and properties of the developed electric double layer. The observed discrepancies can also be attributed to the differences in the molecular structure of the examined solutes. The values of the c_2 parameter indicated the importance of the influence of the molecular structure on the processes of ion pairing at the stationary phase and show how important it is to take the molecular structure into account when modeling the retention behavior in chaotropic chromatography systems.

The trend in c_2 and c_3 values observed in the *vI* systems also continued in the *cI* systems. The values of both parameters were drastically lower than in the *vI* system and there was only a slight increase in the investigated pH range. The discrepancies in the calculated c_2 values and [LH] have become smaller and a fairly good agreement among them can be observed in all *cI* systems. Obviously, a higher concentration of Na^+ or NH_4^+ ions suppresses the effect of the mobile phase pH on the adsorption of PF_6^- ions, leading to a lower ion pairing at the stationary phase and consequently to lower c_2 values. Although both K^+ and NH_4^+ are inherently chaotropic, it can be hypothesized that only NH_4^+ exerts this effect on protonated basic solutions, and only when the concentrations are quite high, as in the *cI* system. Although the [LH] values were lower in the NH_4^+ systems compared to the K^+ systems, the calculated c_2 values were quite similar for all solutes, and in the case of loratadine, they were the highest compared to the other two systems.

Conclusions

In this study, the effects of the counterion, of both the chaotropic agent and the ionic strength modifier, on the retention behavior of 23 fully protonated basic solutes in chaotropic chromatography were investigated in the experiments with variable (*vI*) and constant ionic strength (*cI*). Three different chaotropic salts ($NaPF_6$, KPF_6 and NH_4PF_6) were used, with the addition of NaCl, KCl and NH_4Cl in the *cI* experiments. For an effective and unambiguous description of the observed retention behavior, the extended thermodynamic approach was applied. In both *vI* and *cI* systems, higher values of c_2 and

c_3 are observed at higher pH values of the mobile phase, but the c_3 values were drastically lower compared to c_2 under the same experimental conditions. The KPF_6 *vI* systems differed as the c_2 values were significantly higher compared to the c_2 values in *vI* systems with $NaPF_6$ and NH_4PF_6. Although both K^+ and $NH4^+$ are chaotropic in nature, the c_2 values of the *cI* systems led to the hypothesis that only quite high NH_4^+ concentrations exert this effect on protonated basic solutes. Ion-pair formation in the stationary phase was favored by the presence of high $NH4^+$ concentrations and the differences in *c2_vI* and *c2_cI* values are not so pronounced as in the other two systems with $NaPF_6$ and KPF_6.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

A.M.: Conceptualization, Supervision, Writing - review & editing; **K.G.**: Formal analysis, Writing - original draft, **M.R.**: Formal analysis; **A.P.**: Data curation, Writing - review & editing; **Y.D.**: Conceptualization, Supervision, Writing - review & editing.

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Primena proširenog termodinamičkog pristupa za opisivanje efekta katjona haotropnih agenasa i modifikatora jonske jačine na retenciono ponašanje protonovanih analita baznih osobina u haotropnoj hromatografiji

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Kratak sadržaj

U ovom radu, primenjen je prošireni termodinamički pristup kako bi se kvantitativno objasnio efekat katjona haotropnih agenasa i modifikatora jonske jačine, u sistemima varijabilne (*vI*) i konstantne jonske jačine (*cI*) na retenciono ponašanje 23 potpuno protonovana analita baznih osobina. Sprovedeno je devet serija eksperimenata (pri tri pH vrednosti za $NaPF_6$, KPF_6 i NH_4PF_6) sa *vI* i devet serija eksperimenata (pri tri pH vrednosti za $NaPF_6$, KPF_6 i NH_4PF_6) sa jonskom jačinom koja je održavana konstantnom sa NaCl, KCl i NH_4Cl. Eksperimentalno određeni retencioni faktori modelovani su primenom proširenog termodinamičkog pristupa i objašnjeni su procesi koji se odigravaju na stacionarnoj fazi i u mobilnoj fazi, kao i njihov uticaj na retenciju u ispitivanim sistemima haotropne hromatografije. Pokazalo se da je, i u *vI* i u *cI* sistemima, formiranje jonskih parova na stacionarnoj fazi dominantno u odnosu na formiranje jonskih parova u mobilnoj fazi. U sistemima KPF6_*vI* ove interakcije sa stacionarnom fazom bile su još izraženije nego u drugim sistemima. Iako su i K^+ i $NH4^+$ haotropne prirode, formiranje jonskih parova na stacionarnoj fazi je favorizovano prisustvom $NH4^+$ samo pri visokim koncentracijama ovog katjona kao što je u *cI* sistemima.

Ključne reči: prošireni termodinamički pristup, haotropna hromatografija, retenciono ponašanje, efekat katjona

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