

Interaction of Thiosemicarbazides with Cyanopropyl Silica Gel

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Received April 17, 2019; revised April 21, 2019; accepted April 24, 2019

Abstract—The interaction of ethyl-, allyl-, and phenyldimethylthiosemicarbazide with silica gel with grafted cyanopropyl groups has been studied in aqueous and organic solutions under the conditions of normal- and reversed-phase liquid chromatography. The influence of liquid phase composition and temperature on the separation of reaction mixtures of thiosemicarbazides and isothiocyanates in a Zorbax-CN column has been investigated. The elution order of ethyl-, allyl-, and phenyldimethylthiosemicarbazide has been found to be the same when using their aqueous and organic solutions. The selectivities of silica gels with grafted cyanopropyl and octadecyl groups have been compared. Thermodynamic parameters have been determined for the adsorption of the thiosemicarbazides on the modified silica gels.

DOI: 10.1134/S1061933X19050181

INTRODUCTION

The interest in thiosemicarbazides and their derivatives is due to the fact that this class of substances includes many biologically and physiologically active compounds [1]. Thiosemicarbazides exhibit antibacterial, antitumor, anti-inflammatory, fungicidal, insecticidal, and herbicidal activities and can play the role of phytohormones [1–3]. They are polyfunctional compounds containing several reactive sites (nitrogen and sulfur atoms and combinations thereof). The dinucleophilic properties of thiosemicarbazides make it possible to widely use them for the synthesis of biologically active triazoles, pyrazoles, oxazoles, thiadiazines, triazines, and other nitrogen-containing heterocycles [1]. Moreover, thiosemicarbazides are capable of complexation with metal cations and are widely applied for detecting Pt, Cd, Ni, and Hg [4]. In [5, 6], thiosemicarbazides were proposed to be used as derivatives of alkylhydrazines when performing the chromatographic analysis of asymmetric dimethylhydrazine in environmental objects, while their interaction with hydrophobic sorbents (poly(dimethylsiloxane) and porous graphitized carbon) was studied under the conditions of gas and liquid chromatography.

Cyanopropyl silica gel, i.e., silica gel containing grafted cyanopropyl groups ($\text{SiO}_2\text{-RCN}$), is a moderate-polarity sorbent, although an RCN group has a rather high dipole moment (4.0 D) [7]. However, as has been noted in [8, 9], the polarity of sorbents does not completely correlate with the polarity of grafted organic compounds because of the interference of grafted groups and their interaction with a sorbent surface and a solvent. In contrast to silica gel, cyanopropyl silica gel is hydrolytically stable at pH 1–8; there-

fore, it may be successfully used for the analysis of polar compounds in systems comprising aqueous and organic solvents by normal- and reversed-phase high-performance liquid chromatography (NP HPLC and RP HPLC, respectively), as well as by hydrophilic chromatography [8–12]. A layer of grafted cyanopropyl radicals has a “brushlike” structure; i.e., the radicals are oriented normal to a surface in contrast to a layer of octadecyl radicals, where they are arranged chaotically (disorderedly) with respect to the silica gel surface. Moreover, RCN groups may interact with residual OH groups of modified silica gel to yield arch-like structures [8]. The presence of dipoles in the form of CN groups facilitates the ionic and coordination interactions with polarizable compounds. It has been found [8] that the selectivities of benzene and hexane retention on $\text{SiO}_2\text{-RCN}$ are almost equal; i.e., the contribution from the specific interaction of the cyan-containing phase with benzene is negligible. Cyanopropyl silica gel may play the role of an acceptor forming weak hydrogen bonds; however, actually no water layer is formed on its surface under the conditions of hydrophilic chromatography [11].

According to [9–12], the sorption properties of $\text{SiO}_2\text{-RCN}$ in NP HPLC resemble the properties of polar silica gel. Both sorbents are used to separate amines, carboxylic acids, alcohols, aldehydes, ketones, pesticides, and drugs in organic media. However, the presence of CN groups sometimes changes the selectivity of the sorbent [10]. The contributions of some functional groups to the retention on $\text{SiO}_2\text{-RCN}$ are nearly five times lower than the corresponding contributions to the retention on silica gel [8]. Therefore, the use of cyan-containing stationary

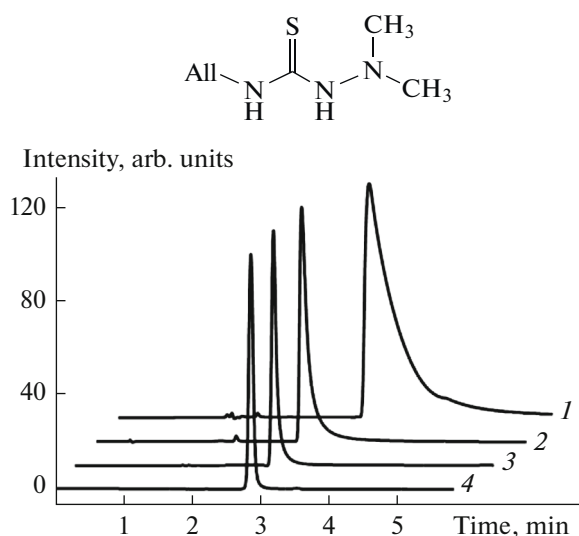


Fig. 1. Dependence of 4-allyl-1,1-dimethylthiosemicarbazide retention time in a Zorbax-CN column on mobile phase composition (30/70, vol/vol): (1) dichloromethane/*n*-hexane, (2) tetrahydrofuran/*n*-hexane, (3) propanol-2/*n*-hexane, and (4) propanol-2/*n*-hexane modified with diethylamine (0.15%).

phases is most advantageous when it is necessary to record several compounds with greatly different polarities in the same chromatogram.

In the regime of RP HPLC, cyanopropyl silica gel is widely used to separate basic, acidic, and neutral compounds in water–organic media. In addition to nonspecific hydrophobic interactions, this sorbent interacts with polar groups of molecules of sorbates and solvents. As a result, the selectivity of systems based on $\text{SiO}_2\text{-RCN}$ differs from the selectivity of traditional systems based on, e.g., octadecyl silica gel ($\text{SiO}_2\text{-C18}$). Under the conditions of RP HPLC, the replacement of octadecyl silica gel by cyanopropyl silica gel may serve as a mean for varying the selectivity of the separation of mixed analyzed compounds similarly to a change in the solvent polarity upon the passage from NP to RP HPLC [8]. The effect of temperature on the retention of compounds on $\text{SiO}_2\text{-RCN}$ remains to be studied; however, information is available that the retention factor must decrease with temperature elevation [8].

The goal of this work was to study the interaction of thiosemicarbazides with cyanopropyl silica gel in aqueous and organic media with the use of NP and RP HPLC and to assess the possibility of using $\text{SiO}_2\text{-RCN}$ for separating mixed thiosemicarbazides and their isolation from isocyanates used as reagents in the synthesis of thiosemicarbazides.

EXPERIMENTAL

Cyanopropyl silica gel packed into a Zorbax-CN column (DuPont Instruments, United States) with sizes of 4.6×150 mm was used as a sorbent. The sorbent had the following characteristics: BET specific surface area, $180 \text{ m}^2/\text{g}$; grain size, $5 \mu\text{m}$; pore diameter, 70 \AA ; and carbon content in the modifier layer, 7%. Silica gel that contained grafted octadecyl groups and was packed into a Zorbax-C18 column (Zorbax Eclipse XDB C18, Agilent Technologies, United States) with sizes of 4.6×150 mm, was used for comparison. This sorbent had the following parameters: BET specific surface area, $180 \text{ m}^2/\text{g}$; grain size, $5 \mu\text{m}$; pore diameter, 80 \AA ; and carbon content in the modifier layer, 20%.

Chromatographic analysis was performed using an Agilent 1200 Series liquid chromatograph equipped with an Agilent G1315B UV photodiode matrix detector employing the ChemStation A.10.02 software package (Agilent Technologies, United States). Chromatographic separations were carried out in the isocratic regime at an eluent rate of $0.5 \text{ mL}/\text{min}$ and an injected sample volume of $20 \mu\text{L}$. Depending on the regime of chromatography, *n*-hexane–propanol-2 mixtures and water containing some amounts of methanol were used as eluents. In addition, tetrahydrofuran, dichloroethane, and diethylamine were used as modifiers. All solvents (Sigma-Aldrich, United States) were of the HPLC grade. The compounds were identified using their absorption at 240 nm [6].

4-Ethyl-1,1-dimethylthiosemicarbazide (I), 4-allyl-1,1-dimethylthiosemicarbazide (II), and 4-phenyl-1,1-dimethylthiosemicarbazide (III) were obtained via the interaction of 1,1-dimethylhydrazine with ethyl-, allyl-, and phenylisothiocyanate (RNCS, where *R* is Et, All, and Ph, respectively) at room temperature [5, 6].

RESULTS AND DISCUSSION

Figure 1 presents the data on the effect of mobile phase composition on the chromatographic behavior of 4-allyl-1,1-dimethylthiosemicarbazide II in a Zorbax-CN/*n*-hexane system, with the solvent containing additives of different organic modifiers (dichloromethane, tetrahydrofuran, propanol-2, and diethylamine).

The experiments carried out under the conditions of NP HPLC have shown that the trailing edge of the chromatographic peak for thiosemicarbazide II is rather strongly diffused (Fig. 1), thereby decreasing the Zorbax-CN column resolution. Under the conditions of equilibrium chromatography, the asymmetry of a peak indicates that the adsorption isotherm deviates from linearity [12]. A peak with a sharp leading edge and a diffused trailing edge corresponds to a convex adsorption isotherm of the thiosemicarbazide, i.e., characterizes a rather strong interaction of the substance with cyanopropyl silica gel. To weaken the

interaction of the thiosemicarbazide with the sorbent, organic modifiers were added to *n*-hexane. The sorption characteristics and selectivity of the separation of analyzed compounds can be varied in a wide range by varying solvent composition. In the series *n*-hexane → dichloromethane → tetrahydrofuran → propanol-2, solvent solvatochromic parameter β (according to Kamler and Taft [7]) increases as follows: 0 → 0.10 → 0.55 → 0.95. These modifiers, especially propanol-2, are able of competing with the thiosemicarbazide for a site on the surface of the $\text{SiO}_2\text{-RCN}$ stationary phase, which contains residual silanol groups, and interacting with the thiosemicarbazide, thereby altering the equilibria that take place in the system. As can be seen in Fig. 1, the use of the modifiers makes the chromatographic peak for compound **II** more symmetric. Mobile phase composition has a similar effect on chromatographic peak shapes for thiosemicarbazides **I** and **III**.

The best results and the shortest retention times for compounds **I–III** have been obtained using a mixture of propanol-2 with *n*-hexane additionally modified with diethylamine (0.15%), which reduces the effect of residual acidic silanol groups present in the $\text{SiO}_2\text{-RCN}$ surface layer on thiosemicarbazide sorption. This eluent was further used to separate thiosemicarbazides from reaction mixtures with isothiocyanates, which are used in excess for the synthesis of the thiosemicarbazides.

Figure 2 illustrates the results of chromatographic separating the reaction mixtures of thiosemicarbazides **I–III** with corresponding isothiocyanates. Since isothiocyanates are more polar than thiosemicarbazides, they are retained longer on the $\text{SiO}_2\text{-RCN}$ surface. Therewith, the leading edges of their chromatographic peaks are substantially diffused. This shape of the peaks corresponds to a concave isotherm of the equilibrium adsorption of the isothiocyanates on cyanopropyl silica gel from a given solvent. This shape of the isotherm is caused by the competitive interaction of isothiocyanate molecules with polar components of the mobile phase and with each other [12]. The peaks are especially asymmetric for phenyl- and allylisothiocyanate (Fig. 2, curves 3, 2). These compounds are longer retained on the sorbent surface than ethylisothiocyanate is.

The retention time of thiosemicarbazides also increases with the growth of the hydrocarbon radical in the series **I–II–III**. According to [8–10], the decisive contribution to the retention of the analyzed compounds in the Zorbax-CN column is made by specific interactions of their molecules with the CN groups of the grafted layer. The studied derivatives of thiosemicarbazides (as well as derivatives of isothiocyanates) have similar sets of functional groups; therefore, the differences observed in their retention on the surface of the cyan-containing phase are due to the polarity, electron density, and geometric characteristics of the

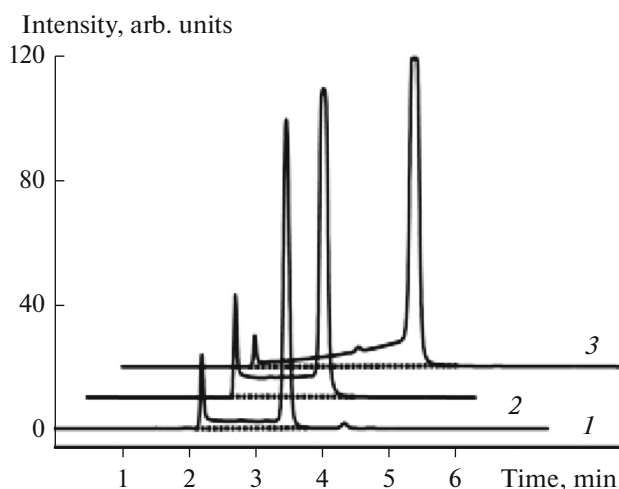


Fig. 2. Chromatograms for the separation of mixtures of thiosemicarbazides (retention times $t_R = 2.2\text{--}3.1$ min) with isothiocyanates ($t_R = 3.5\text{--}5.5$) in a system Zorbax-CN/mixture (30/70, vol/vol) propanol/*n*-hexane modified with diethylamine (0.15%): (1) **I**–EtNCS, (2) **II**–All-NCS, and (3) **III**–PhNCS mixtures.

hydrocarbon radicals. Allyl and phenyl substituents affect the distribution of the electron density in a molecule to a much higher extent than ethyl substituent does. The positive mesomeric effect of allyl and phenyl radicals enhances the separation of the charges in the molecules of the analyzed compounds and their polarizability. The induction effect of ethyl radical is much weaker. Moreover, as has been found in [6], compound **III** interacts with alcohols weaker than two other compounds.

As is seen in Fig. 2, under given conditions of the chromatographic separation in the Zorbax-CN column, the peaks due to the thiosemicarbazides are “masked,” while the peak of **III** can scarcely be detected in the chromatogram. This complicates the separation of thiosemicarbazides and isothiocyanates in reaction mixtures with low contents of desired products and excess amounts of the reagents.

Moreover, weakly polar cyanopropyl silica gel may be considered as a reversed phase; i.e., it may be used in RP HPLC with polar eluents. The efficiency of mixture separation will depend on the ability of the compounds being separated to interact with the mobile and stationary phases while moving along a column. In RP HPLC, retention is predominantly determined by the nonspecific substance–adsorbent interaction and the specific substance–eluent interaction.

Figure 3a depicts an experimental chromatogram obtained when separating mixed thiosemicarbazides in the Zorbax-CN column with the use of an aqueous methanol solution. For comparison, the figure shows an analogous chromatogram recorded with the use of a Zorbax-C18 column filled with silica gel containing

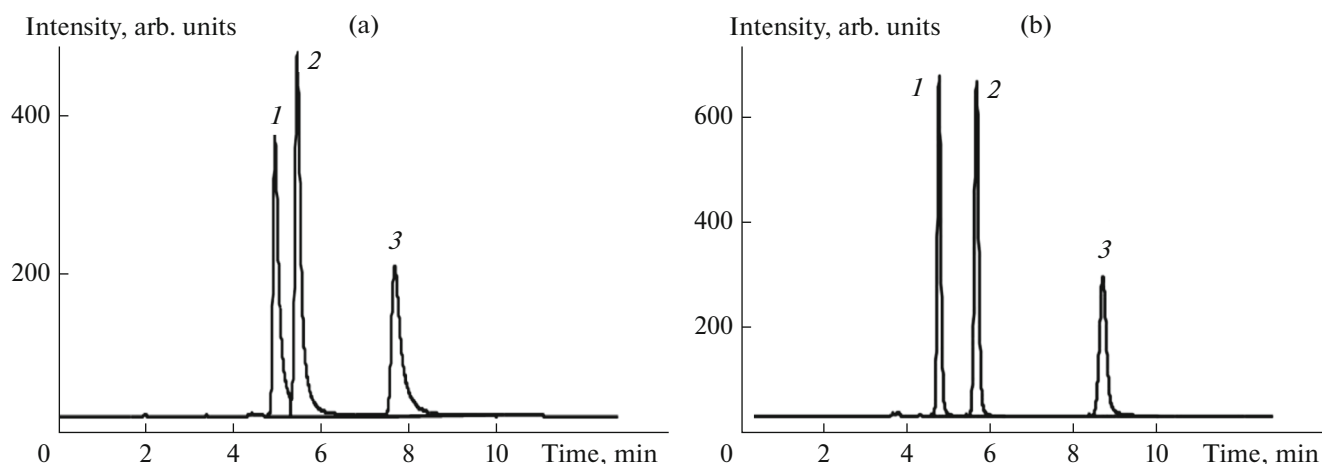


Fig. 3. Chromatograms for the separation of mixed thiosemicarbazides (I) **I**, (2) **II**, and (3) **III** in (a) Zorbax-CN and (b) Zorbax-C18 columns from a methanol/water solution (50/50 vol/vol).

grafted octadecyl radicals (Fig. 3b). It is seen that the order of eluting chromatographic peaks attributed to thiosemicarbazides **I–III** is the same for both chemically modified silica gels; the first and the last peak are due to compounds **I** and **III**, respectively. Lipophilicity factors $\log P$ of the thiosemicarbazides increase in the same series (1.11 \rightarrow 1.30 \rightarrow 2.35), with this factor being most commonly used to characterize the ability of a substance to pass from a nonpolar to a polar phase. The values of $\log P$ are rather close to one another for compounds **I** and **II**, thereby making their separation difficult; however, they substantially differ from $\log P$ calculated for thiosemicarbazide **III**, with the benzene ring making the main contribution to this value. Thus, the larger the nonpolar hydrocarbon moiety and the higher the polarizability of a thiosemicarbazide, the stronger is its retention on cyanopropyl silica gel. An analogous result was previously obtained when separating mixed thiosemicarbazides in a Hypercarb column [6].

The selectivity of a sorbent is determined by the forces of the interaction between sorbate molecules and the sorbent. The selectivity of the sorbents was characterized using separation factor α [12]. The separation factors experimentally determined for the thiosemicarbazides in the Zorbax-CN and Zorbax-C18 columns are $\alpha = 1.3$ and 1.5, respectively. Since $\alpha > 1$, a mixture of thiosemicarbazides may be satisfactorily separated on both sorbents; however, the difference in the lipophilicity factors of compounds **I** and **II** is small (1.11 and 1.30), which may, with a high probability, lead to overlapping of the corresponding peaks. As has been mentioned above, the grafted layer of cyanopropyl radicals has a brushlike structure; therefore, the planar shape of compound **II** molecules has a weaker effect on the sorption than does this effect in the case of Hypercarb carbon sorbent.

The selectivity of the separation of compounds **I** and **II** may be increased by varying the polarity of an eluent. The retention of the studied compounds was characterized using retention factor k . Figure 4 shows the dependences of reciprocal retention factors $1/k$ of thiosemicarbazides **I–III** on methanol volume fraction φ in water. The retention of the thiosemicarbazides on cyanopropyl silica gel weakens with an increase in methanol content, i.e., with an increase in the polarity of the mobile phase. The nonlinear pattern of the $1/k = f(\varphi)$ dependence confirms the strong intermolecular interaction of compounds **I** and **II** with methanol. Thiosemicarbazide **III** interacts with methanol weaker than two others, and eluent composition affects its retention much weaker. The effect of solvent composition on the retention of the thiosemicarbazides on Zorbax-C18 is similar.

The equations of the $1/k = f(\varphi)$ dependence for the retention of compounds **I–III** in the Zorbax-CN column are as follows (r^2 is the determination coefficient):

$$1/k_{\text{I}} = 0.0025\varphi^2 - 0.1278\varphi + 2.4431 \quad (r^2 = 0.9992),$$

$$1/k_{\text{II}} = 0.0023\varphi^2 - 0.1257\varphi + 2.3729 \quad (r^2 = 0.9994),$$

$$1/k_{\text{III}} = 0.0014\varphi^2 - 0.0856\varphi + 1.5330 \quad (r^2 = 0.9993).$$

These equations enable one to predict the chromatographic behavior of the thiosemicarbazides when using the Zorbax-CN column and eluents with different contents of methanol in water.

As can be seen in Fig. 5, the retention factor of thiosemicarbazides in the Zorbax-CN column varies linearly with an increase in the number of carbon atoms n_C in their hydrocarbon radicals. The obtained dependence is described by the equation $\ln k = 0.2513n_C - 1.2986$ ($r^2 = 0.9999$). An analogous dependence for the retention of the thiosemicarbazides on

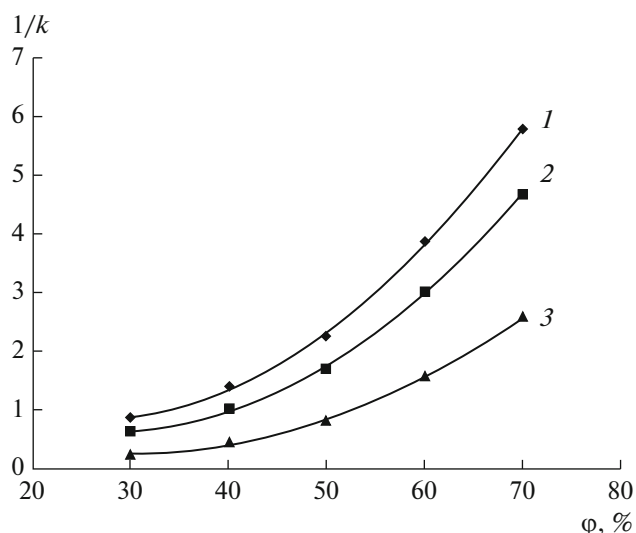


Fig. 4. Dependences of reciprocal retention factor $1/k$ on volume fraction ϕ of methanol in water for thiosemicarbazides (1) I, (2) II, and (3) III in the Zorbax-CN column.

Zorbax-C18 is located somewhat higher (curve 2): $\ln k = 0.2788n_C - 0.8939$ ($r^2 = 0.9884$).

A study of the effect of temperature on a chromatographic system makes it possible to determine the thermodynamic characteristics of the sorption process. Figure 6 presents the experimental temperature dependences for the factors of retention of thiosemicarbazides I–III on Zorbax-CN. These dependences are linear for all three compounds in a rather wide temperature range $T = 298$ – 318 K (determination coefficient is $r^2 = 0.9974$ – 0.9993). As the temperature is elevated, the retention of the thiosemicarbazides regularly decreases; however, no change is observed in the selectivity of the process. Due to the significant differences between the values of $\ln k$, mixture of compounds I–III can be efficiently separated throughout the studied temperature range.

The values of the enthalpy, entropy constant, and temperature coefficient of the sorption of thiosemicarbazides I–III on silica gels with grafted CN and C18 groups (Table 1) were determined from the experimental $\ln k = f(1/T)$ dependences by the equation $\ln k = -\Delta H^\circ/RT + \Delta S^\circ/R + \ln \phi$. Temperature coefficient $V = [(k_1 - k_2) - 1]/(T_2 - T_1)$ of the sorption (Table 1) shows a change in the retention factor of a substance upon a change in the temperature by 1 K. This information may be useful for increasing the efficiency of the separation of thiosemicarbazides, because a rise in the working temperature of columns is a convenient mean for decreasing the viscosity of a mobile phase and the pressure in a column.

As follows from the data presented in Table 1, an increase in the temperature by 1 K entails a change in the retention of the thiosemicarbazides in the Zorbax-CN and Zorbax-C18 columns by 1–1.8 and 0.6–

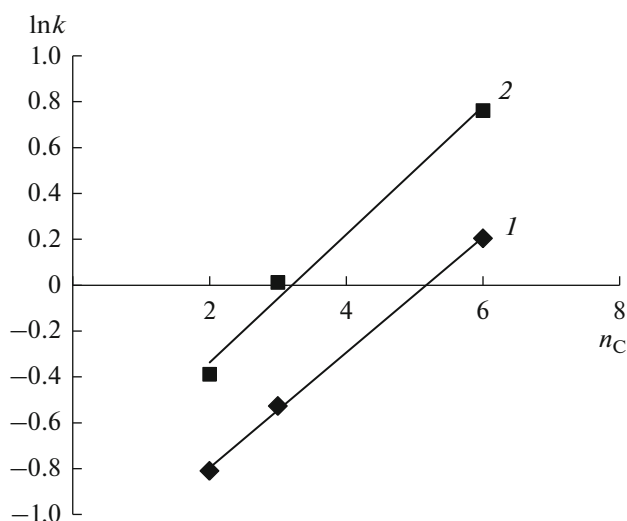


Fig. 5. Logarithmic factors k of retention on (1) Zorbax-CN and (2) Zorbax-C18 sorbents as functions of number n_C of carbon atoms in hydrocarbon radicals of thiosemicarbazides I–III.

1.2%, respectively; i.e., the reproducibility of the retention times for compounds I–III is somewhat worse in the Zorbax-CN column. This column should be thermostated to attain a long-term reproducibility of the retention times in it.

The values of the thermodynamic characteristics for the adsorption of compounds I–III on Zorbax-CN are higher than those on Zorbax-C18; i.e., the interaction of the thiosemicarbazides with cyanopropyl silica gel is stronger than that with octadecyl silica gel. This is associated with the realization of a complex mechanism of the retention of these compounds on SiO_2 -RCN, with the retention being dependent on

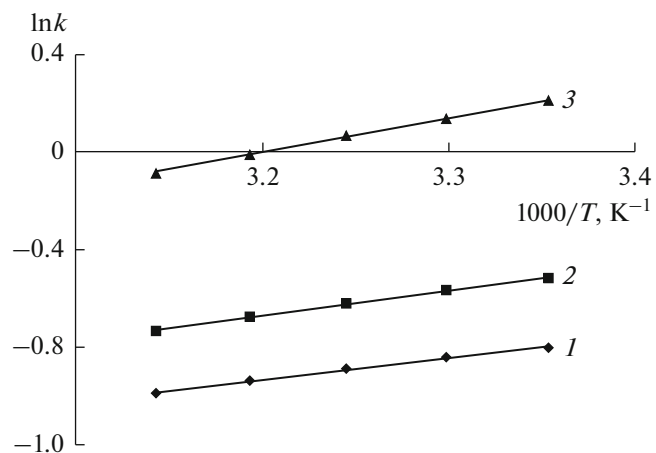


Fig. 6. Experimental temperature dependences of logarithmic retention factor $\ln k$ for thiosemicarbazides (1) I, (2) II, and (3) III in a Zorbax-CN column.

Table 1. The values of enthalpy, entropy constant, and temperature coefficient for the sorption of thiosemicarbazides I–III in Zorbax-CN and Zorbax-C18 columns

Column	Compound	$-\Delta H^\circ$, kJ/mol	$-\Delta S^\circ/R + \ln\phi^*$	$V \times 10^3$, K $^{-1}$
Zorbax-CN	I	7.4	3.8	10
	II	8.6	4.0	12
	III	11.6	4.6	18
Zorbax-C18	I	4.2	2.0	6
	II	5.3	2.1	7
	III	8.8	2.5	12

* The uncertainty is caused by the fact that the manufacturer has not reported the free volumes of the chromatographic columns.

both specific and hydrophobic sorbate–sorbent interactions.

The performed studies of the interaction of different thiosemicarbazides with cyanopropyl silica gel have resulted in the selection of optimal conditions for the chromatographic separation of these compounds and their mixtures with isothiocyanates that are used as reagents for the synthesis of the thiosemicarbazides. An interesting regularity has been revealed for cyanopropyl silica gel—its selectivity with respect to the separation of mixed ethyl-, allyl, and phenylthiosemicarbazides remains almost unchanged upon the passage from a nonpolar eluent to a polar one. That is, the order of the eluting the thiosemicarbazides upon the separation of their mixtures in a Zorbax-CN column under the conditions of NP and RP HPLC is predominantly determined by the nature of a grafted cyan-containing phase.

CONCLUSIONS

The interaction of ethyl-, allyl-, and phenylthiosemicarbazides with silica gel containing grafted cyanopropyl groups has been studied under the conditions of normal- and reversed-phase liquid chromatography. The selectivity of the separation of ethyl-, allyl-, and phenylthiosemicarbazides in a SiO₂–RCN column weakly depends on the polarity of an eluent, while the order of the elution of the thiosemicarbazides upon the separation of their mixtures in the NP and RP HPLC regimes is mainly governed by the nature of a grafted layer of cyanopropyl radicals.

The retention of the compounds from aqueous and organic solutions in the Zorbax-CN column becomes stronger in the series 4-ethyl-1,1-dimethylthiosemicarbazide → 4-allyl-1,1-dimethylthiosemicarbazide → 4-phenyl-1,1-dimethylthiosemicarbazide. The effects of mobile phase composition and temperature on the separation of mixed thiosemicarbazides have been studied. The selectivity of silica gel with grafted cyanopropyl groups has been compared with that of silica gel with octadecyl groups. It has been shown that the order of eluting the thiosemicarbazides from the

mixtures is the same in the Zorbax-CN and Zorbax-C18 columns. The thermodynamic parameters have been determined for the sorption of the thiosemicarbazides on the chemically modified silica gels.

The performed studies have resulted in optimizing the chromatographic separation of mixed thiosemicarbazides and determining the conditions for the separation of their reaction mixtures with isothiocyanates that are used as reagents for the synthesis of the thiosemicarbazides.

ACKNOWLEDGMENTS

We are grateful to the Center for Collective Use of the Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, for letting us use experimental equipment.

FUNDING

This work was carried out within the framework of a state order to the Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, and supported by the Russian Foundation for Basic Research, projects nos. 18-08-01224 and 17-08-00315.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Translated by A. Kirilin