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Sorption of Quinoline Derivative under Conditions of Liquid Chromatography

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Abstract—Laws governing the sorption of quinoline derivatives on hypercrosslinked polystyrene are studied under conditions of reverse-phase high-performance liquid chromatography. Factors of sorbate retention at different concentrations of acetonitrile in the eluent are determined. An analysis is performed of the dependences of variation in the enthalpy of sorption and the entropy term of the temperature dependence of the retention factor on the content of the organic component in the eluent for the studied compounds.

Keywords: reverse-phase high-performance liquid chromatography (RP-HPLC), sorption, quinoline derivatives, hypercrosslinked polystyrene, thermodynamic characteristics of sorption

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INTRODUCTION

The rapid development of the theory and practice of liquid chromatography shows this technique has enormous potential as an analytical tool and an effective way of determining different physicochemical characteristics of substances and the relationship between their retention and structure [1, 2]. The possibility of using chromatography to solve the inverse problem—determining the structural features of sorbed molecules according to their sorption characteristics (so-called chromatography, as defined by Kiselev [3])—is of growing interest. The algorithm for solving this problem was developed mostly for conditions of gas chromatography, since the problem in liquid chromatography must be solved by allowing for many factors (e.g., the nature and composition of the eluent, and the possibility of different processes occurring in a bulk eluent solution) that greatly complicate calculations. A basis for solving this problem is determining the types of intermolecular interactions of different origin that occur under conditions of liquid chromatography, since the retention of sorbates and their selectivity toward separation in these systems are determined by a wide variety of specific and non-specific interactions, and different combinations of them [4].

A combination of theoretical and experimental means should be considered optimal for these studies. It is obvious that a discrepancy between the obtained data can indicate either a flaw in the chosen theoretical model and the methodology of theoretical calculations or the inaccuracy or insufficiency of experimen-

tal data and available information on the structure of a molecule. An obvious basis for solving direct and inverse problems of determining the relationship between structure and chromatographic retention is accumulating an array of data on the structure and retention of substances of different structures for different chromatographic conditions [5]. A considerable number of recent reports have focused on studying this relationship for heterocyclic compounds. The diversity of the structures of these compounds and the different types of biological activity they exhibit make these substances convenient materials for solving the problem [6–8].

The attention given to quinoline derivatives as heterocycles can be attributed to the broad range of important practical properties exhibited by these substances [9, 10]. The structural diversity of quinolines is associated with their structure containing reduced and/or aromatic heterocyclic moieties, functional groups, and substituents of different chemical origins. This in turn contributes to a wide variety of intermolecular interactions between these substances and components of a liquid chromatography system.

This work focuses on the laws governing the sorption of quinoline derivatives from water–acetonitrile solutions on hypercrosslinked polystyrene (HCPS) under conditions of reverse-phase high-performance liquid chromatography (RP-HPLC).

EXPERIMENTAL

Our analysis was performed on a Milichrome A02 liquid chromatograph equipped with a UV spectrometric detector. Detection was at a wavelength of 254 nm. The sorbent was monodisperse HCPS with a 150% degree of crosslinking. The particle size was 3.2 μm , and the column dimensions were 150 \times 3 mm. The experiment was conducted in the 298–328 K range of temperatures.

Elution was done in an isocratic mode. Acetonitrile–water mixtures with 50, 60, and 80% volume fractions of acetonitrile were used as the mobile phase. The volumetric flow rate of the eluent was 500 $\mu\text{L}/\text{min}$. The mobile phases were prepared using triply distilled water and HPLC-gradient grade acetonitrile (Panreac, Spain). Degassing was done by exposing the prepared water–acetonitrile mixtures to ultrasound on a UZDN-2T unit.

A sorbate sample was prepared by dissolving the crystalline substance in an appropriate mobile phase. The retention of the studied compounds was characterized by retention factor (k), calculated using the formula

$$k = \frac{t_R - t_M}{t_M},$$

where t_R is the period of retention for the analyte and t_M is the one for the nonsorbable substance (sodium nitrite). The error of determination did not exceed 2%.

The formulas of the studied compounds, the experimental retention factors averaged over 5–7 values, molar volume V , polarizability α , and dipole moments μ , calculated using the HyperChem 8 Professional software, are listed in Table 1.

The thermodynamic characteristics of sorption of the studied quinoline derivatives were calculated using the equation

$\ln k = -\Delta H^\circ/RT + \Delta S^\circ/R + \ln \phi = -\Delta H^\circ/RT_c + A$,
where ΔH° and ΔS° are the standard molar changes in enthalpy and entropy upon the sorbate moving from the bulk solution to the surface layer, ϕ is the phase ratio of the column, and A is the entropy term [11]. The relative error of determination was 1–3%.

RESULTS AND DISCUSSION

It is known that in the RP-HPLC mode, substances are retained mostly due to forces of dispersion and hydrophobic [12]. At the same time, some sorbents used in this version of liquid chromatography (e.g., HCPS, porous graphitized carbon) are capable of other types of interactions that strongly affect the chromatographic process. It is therefore known that porous graphitized carbon is characterized by the polar retention effect, which manifests as the predominant retention of polar sorbates [13]. With sorption on HCPS, a major contribution to retention is made by

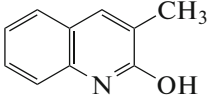
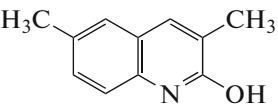
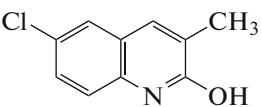
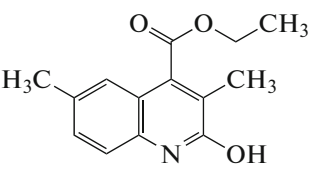
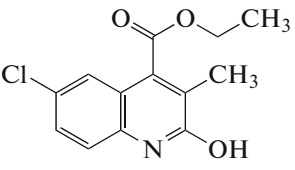
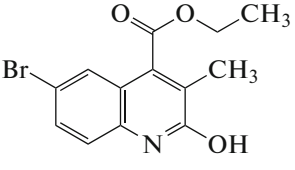
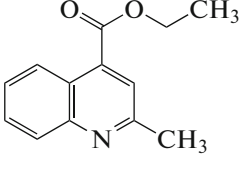
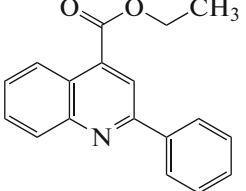
specific π -interactions that can involve sorbate molecules which include aromatic moieties, unsaturated bonds, and substituents with vacant d -orbitals or electron lone pairs [14].

Since interactions other than those of dispersion can occur in these chromatographic systems, the retention of many heterocycles (particularly quinoline derivatives) on these sorbents is characterized by a number of features determined by both the structure of the heterocycle molecules and the nature of the sorbent [7, 15, 16]. There are several structural features of quinoline derivatives responsible for their participation in different types of intermolecular interactions that occur in the chromatographic process. These include the aromaticity of the pyridine moiety in the quinoline molecule. This is confirmed by the energy of delocalization, which is comparable to the one in the benzene molecule (134 and 151 kcal/mol, respectively). The nitrogen atom in the structure of this molecule displays negative mesomeric and inductive effects and acts as an electron-acceptor substituent [17]. The molecules of quinoline derivatives generally have a fairly high affinity for protons, and the structure of possible protonated complexes and the distribution of the charges in them are determined mostly by the nature and position of the substituents. Positions 2 and 4 of the quinoline ring are characterized in particular by a lower electron density than that of positions 3, 5, 6, and 8. The properties of the alkyl groups at these positions are similar to those of the alkyls bound to typically aromatic rings [18]. The activities of the hydrogen atoms of the methyl groups localized at positions 2 and 3 of quinoline and the chlorine atoms at positions 2 and 4 differ. The activity of the functional groups at position 4 depends largely on, e.g., the nature and position of other functional groups in the molecule.

The condensed aromatic system of quinoline with a nitrogen atom and the presence of substituents of different chemical origins are thus responsible for the nonuniform distribution of electron density in the molecules of quinoline derivatives that combine the properties of a hydrogen donor and an electron donor and are capable of strong dispersion along with π - π and other specific interactions.

The quinoline derivatives chosen for this work contained alkoxy groups at position 4, substituents of different chemical origins at positions 2 and 6 of the quinoline nucleus, and methyl at position 3. As noted above, these substituents contribute to the redistribution of electron density in the main quinoline nucleus, but the parameters of the studied substances (volume, polarizability, dipole moment) did not change appreciably upon moving from one substance to another; on average, they were on the same order of magnitude. The range of variation in the molar volume of the studied derivatives was 169.7–303.1 \AA^3 ; the polarizability and the dipole moment varied in the range of

Table 1. Retention factor (*k*) at different acetonitrile concentrations in the eluent and physicochemical characteristics of sorbates

No.	Formula	<i>k</i>			<i>V</i> , Å ³	α , Å ³	μ , D
		50%	60%	80%			
1		2.86	1.99	1.47	169.7	53.15	1.32
2		4.56	2.90	2.02	187.7	54.64	1.49
3		7.28	4.39	2.78	182.8	54.27	1.02
4		4.69	3.35	1.88	253.8	60.03	1.84
5		6.48	5.34	2.76	249.0	59.67	1.74
6		11.01	7.01	3.46	253.5	59.99	1.83
7		5.08	3.33	2.06	238.0	59.92	3.01
8		33.33	16.19	7.27	303.1	42.80	2.89

The substances are numbered below in accordance with Table 1.

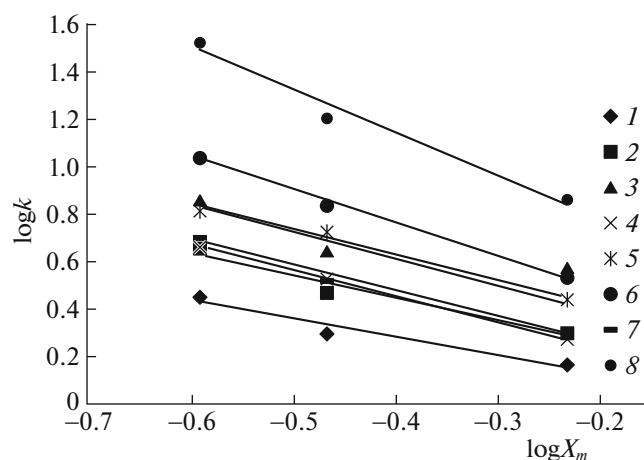


Fig. 1. Dependences of the retention factor of quinoline derivatives (1–8) on the concentration of acetonitrile ($T = 298$ K).

42.8–60.03 Å³ and 1.02–3.01 D, respectively. Since retention in RP-HPLC is determined mostly by dispersion interactions between the sorbate molecules and the stationary phase, it was reasonable to expect similar values of retention for the studied compounds. However, it was found that the range of retention factors of the substances was wider and (as expected) depended on both the structure of the sorbate molecules and the composition of the mobile phase.

It is evident from the data shown in Table 1 that the minimum retention factor was that of substance **1** with the minimum molar volume value. The addition of methyl at position 6 (substance **2**) contributed to an increase in retention by a factor of ~1.5, relative to that of substance **1** at comparable volumes, even though it had a slightly higher polarity that should have enhanced interaction with components of the mobile phase. Switching from substance **2** to **3**, from **4** to **5**, and then to substance **6**, while replacing methyl with chlorine atoms and then bromine atoms, raised the

Table 2. Parameters of the Snyder–Sochevinsky equation ($T = 298$ K)

Substance	a	n	R^2
1	–0.033	0.789	0.952
2	0.061	0.965	0.956
3	0.157	1.141	0.960
4	0.070	1.119	0.999
5	0.198	1.070	0.983
6	0.201	1.408	0.998
7	0.047	1.081	0.982
8	0.412	1.822	0.980

retention factors of halogen-containing derivatives considerably, relative to those of their counterparts, despite the close values of all parameters of these pairs of substances. The increased retention of halogen-substituted quinolines was probably due to the additional contribution from specific interactions of the halogen atoms to the total energy of sorbate–HCPS intermolecular interaction, which is characteristic of the sorption of the respective derivatives and other heterocycles [19].

The emergence of an ester group in the molecules of substances **4** and **5** led to a considerable increase in molecular volume, polarizability, and dipole moment. However, it was found the retention factors of these substances were comparable to the respective values of their structural counterparts **2** and **3**. The retention of the ester counterparts exhibits two tendencies probably associated with this group. On the one hand, the hydrophobic hydrocarbon radical in the ester contributes to the expulsion of sorbate molecules from the polar mobile phase to the sorbent's surface and thereby enhances retention. On the other hand, the higher polarity of ethoxy derivatives and the carbonyl oxygen atom prone to interacting with the polar components of the mobile phase weaken the interaction with the sorbent and thereby reduce the retention factor.

According to Table 1, the retention factor diminished when the concentration of acetonitrile in the eluent was raised, which is consistent with the laws governing retention in the RP version of HPLC. However, the type of the dependence characterizing the effect the composition of the eluent has on retention can differ, depending on the nature and structure of the eluted substances and those of the eluent and sorbent. One of the simplest and therefore most frequently used models for describing the effect the composition of the mobile phase has on chromatographic retention is the Snyder–Sochevinsky model, which approximates these relationships with the linear dependence $\log k = a - n \log x_m$ [12]. However, it is known that considerable deviations from linearity can be observed during chromatography with compounds capable of specific interactions with mobile phase components [7, 20].

Figure 1 shows plots of the dependence of the retention factor of quinoline derivatives on the acetonitrile concentration in the eluent in the coordinates of the Snyder–Sochevinsky displacement model. Table 2 lists coefficients of the respective equations.

The data suggest that in the selected range of concentrations, this dependence is linear for all compounds with a coefficient of correlation of 0.952–0.999.

Coefficient n , which is known to be interpreted in terms of the Snyder–Sochevinsky model as the number of solvent molecules displaced from the sorbent surface by sorbate molecules, in this case changed

Table 3. Standard differential molar changes in the enthalpy (ΔH° , kJ/mol) and the entropy term at different molar fractions x of acetonitrile in the eluent

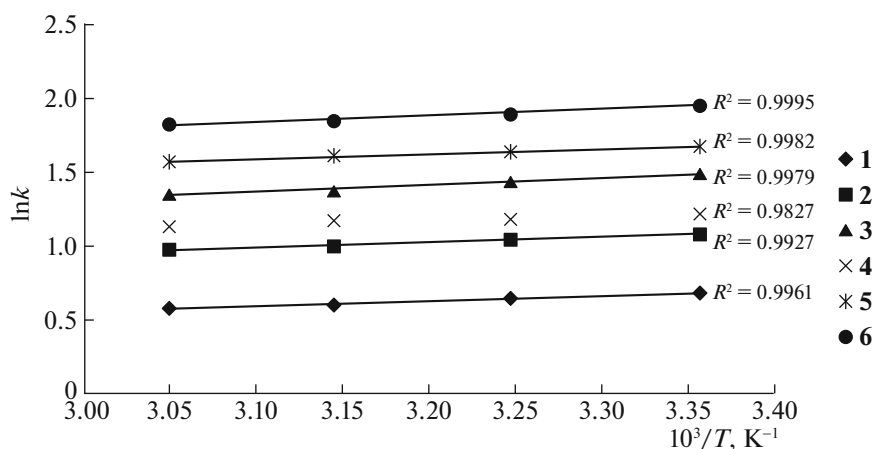
Substance	$x = 0.257$		$x = 0.341$		$x = 0.580$	
	$-\Delta H^\circ$	A	$-\Delta H^\circ$	A	$-\Delta H^\circ$	A
1	1.46 ± 0.03	0.46 ± 0.01	2.87 ± 0.01	-0.47 ± 0.01	3.95 ± 0.04	-1.21 ± 0.03
2	1.25 ± 0.04	1.01 ± 0.03	3.08 ± 0.02	-0.17 ± 0.01	4.36 ± 0.06	-1.05 ± 0.02
3	1.99 ± 0.07	1.18 ± 0.04	3.76 ± 0.01	-0.04 ± 0.00	5.08 ± 0.02	-1.03 ± 0.03
4	2.27 ± 0.03	0.63 ± 0.01	2.17 ± 0.04	0.33 ± 0.01	3.45 ± 0.03	-0.76 ± 0.02
5	2.42 ± 0.05	0.89 ± 0.02	2.87 ± 0.01	0.52 ± 0.02	4.82 ± 0.05	-0.93 ± 0.02
6	3.34 ± 0.03	1.05 ± 0.01	3.74 ± 0.01	0.43 ± 0.01	5.18 ± 0.03	-0.85 ± 0.02

from a minimum value of 0.789 for substance **1** with a minimum volume to a maximum value of 1.822 for substance **8** with the maximum molecular volume. At the same time, the number of mobile phase molecules displaced from the sorbent surface differed somewhat: for substances **4** and **6** with almost identical volume values (253.8 and 253.5), 1.119 and 1.408, respectively. In contrast, the n values are quite similar for pairs of substances **3** and **4** or **3** and **5** with different molecular volumes. This discrepancy between the volumes of sorbed analyte molecules and the n value (the number of displaced molecules of the organic component of the mobile phase) can apparently be attributed to differences in the contact area between sorbed molecules of different origins and the sorbent's surface, which is in turn determined by the energetically preferable orientation of the molecule relative to this surface.

The variability of this orientation during sorption from a water–acetonitrile solution was due mainly to the stereochemistry of the respective molecules: only separate portions of nonplanar sorbate molecules typically come into contact with the sorbent's surface as a result of steric hindrances. Lower values of coefficient n are also characteristic of more polar sorbates that

experience the orientation effect of the polar components of the eluent, which are capable of turning the molecules relative to the sorbent's surface in accordance with the energetically more favorable orientation of the resulting sorption complex. As a consequence, the molecules will interact only with the most hydrophobic portion of this surface. The possibility of this change in the orientation of sorbed molecules relative to the sorbent's surface was shown earlier for ester and carboxyl derivatives of tetrahydroquinoline, for which quantum chemical calculations were made to show that the orientation of molecules by carbonyl oxygen toward the solution is energetically more favorable for sorption from a water–acetonitrile eluent. It reduces the area of contact between these molecules and the sorbent's surface and thereby weakens retention [21].

Raising the temperature predictably lowers the retention factor of the studied compounds, as can be seen from the plots of the respective dependence shown in Fig. 2. The data suggest that in the selected range, the temperature dependence of retention factor can be approximated by a linear equation with a coefficient of determination of 0.982–0.999.

**Fig. 2.** Temperature dependences of the retention factor of quinoline derivatives **1–6** (content of acetonitrile in the eluent, 60%).

CONCLUSIONS

Values of thermodynamic characteristics of the sorption of the studied substances, determined using the above temperature dependences, are listed in Table 3. It is evident from the data that the enthalpies of sorption were negative for all the substances, testifying to a shift of equilibrium in the chromatographic system toward sorption on an HCPS surface from a water–acetonitrile solution in the selected range of concentrations and the exothermic nature of this process. At the same time, $-\Delta H^\circ$ grows along with the content of acetonitrile in the mobile phase. This change in enthalpy, which is generally not characteristic of sorption under conditions of liquid chromatography, was observed in [22] during the chromatography of some derivatives of 1,3,4-oxadiazole and 1,2,4,5-tetrazine. The authors of [7, 23] observed similar changes in enthalpy during the sorption of heterocycles of a different structure from water–acetonitrile solutions and attributed this to deviation from the competitive mechanism of sorption. Since a high content of acetonitrile in the mobile phase modifies the surface of the sorbent with molecules of this organic component, we may assume the molecules of the analyte do not displace those of the modifier into the bulk solution. Instead, they are sorbed on the surface of the sorbent modified by acetonitrile molecules. The increase in the absolute values of ΔH° upon raising the concentration of acetonitrile in the eluent could be the result of a drop in the additional consumption energy for overcoming the interaction between the organic component and the sorbent by the sorbed molecules. The same factor was probably responsible for the negative values of entropy term A at the maximum concentration of acetonitrile, testifying to a drop in entropy during sorption from a solution of this composition. It should be noted that Saifutdinov et al. [24] also argued this effect can apparently be attributed to enhancement of the swelling of the polymeric adsorbent upon an increase in the concentration of acetonitrile, or to a change in the contributions from hydrophobic and π – π interactions between the sorbate molecules and the sorbent, due to an increase in their solvation.

A final decision about the mechanism of sorption of quinoline derivatives under the chosen conditions of chromatography will probably be made when supplementary experimental data for a wider range of eluent compositions and temperatures become available.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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