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Regularities of the Sorption of 1,2,3,4-Tetrahydroquinoline Derivatives under Conditions of Reversed Phase HPLC

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Abstract—Regularities of the sorption of 1,2,3,4-tetrahydroquinoline derivatives on octadecylsilyl silica gel and porous graphitic carbon from aqueous acetonitrile solutions were investigated. The effect the molecular structure and physicochemical parameters of the sorbates have on their retention characteristics under conditions of reversed phase HPLC are analyzed.

Keywords: reversed phase high-performance liquid chromatography, 1,2,3,4-tetrahydroquinoline derivatives, octadecyl silica gel, porous graphitized carbon

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INTRODUCTION

Among the objects of liquid chromatography studies, quinoline derivatives hold a special place because of their valuable practical properties, which are due mainly to their high biological activity. Other important features of these compounds are their photophysical properties, their ability to improve the performance of fuel, and their antioxidant and anticorrosion properties [1–3].

The complex polyfunctional structure of these compounds also makes them interesting objects for determining the correlation between structure, properties, and chromatographic retention in QSAR/QSPR/QSRR studies [4]. Among these materials, tetrahydroquinoline derivatives containing condensed aromatic rings and saturated heterocyclic fragments are the ones least studied [5]. A feature of the electronic structure of quinoline derivatives is strong interaction between the electronic systems of cyclic structure and the unshared pair of electrons of the heteroatom [6]. The reduced cycle in tetrahydroquinoline results in a lack of conjugation between the aromatic moiety and substituents and thus to the redistribution of electron density, compared to aromatic heterocycles. In addition, the molecular structure of these compounds is deformed and their plane geometry is distorted. This affects their physicochemical properties, including their chromatographic behavior [7]. It is obvious that the planarity or nonplanarity of saturated heterocycles should be most apparent in chromatography on sorbents with flat surfaces, e.g., porous

graphitic carbon (PGC), which is widely used in chromatography [8].

Thus, the aim of this work was to determine the correlation between the structure of tetrahydroquinoline derivatives, their physicochemical characteristics, and their chromatographic retention in reversed phase high-performance liquid chromatography (RP-HPLC).

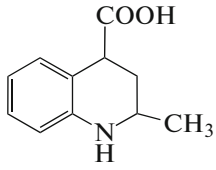
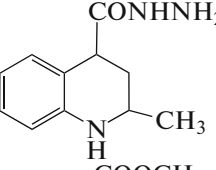
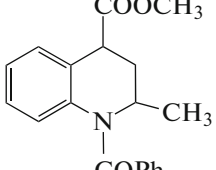
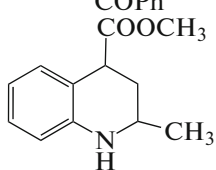
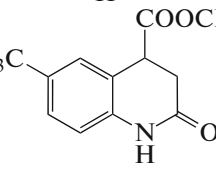
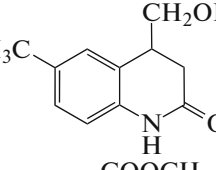
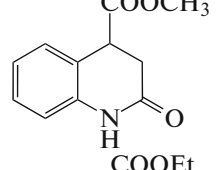
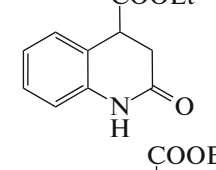
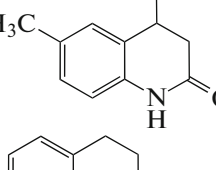
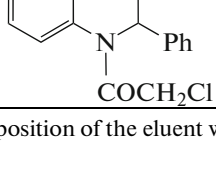
EXPERIMENTAL

Our chromatographic analysis was performed using a Varian liquid chromatograph equipped with a ProStar UV spectrometric detector. Detection was performed at 254 nm. Waters octadecyl silica gel (ODS) (column size, 150 × 4 mm; sorbent grain size, 5 μm) and Hypercarb porous graphitic carbon (column size, 50 × 3 mm; sorbent grain size, 5 μm) were used as sorbents.

The mode of elution was isocratic. A mixture of acetonitrile (40 vol %) and water served as the mobile phase. The volumetric flow rate of the eluent was 500 μL/min. Tridistilled water and HPLC-gradient grade acetonitrile (Panreac, Spain) were used to prepare the mobile phases; the aqueous acetonitrile mixtures were degasified via sonication in a UZDN-2T device. The chromatograms were registered and processed with Galaxie chromatographic analysis software.

Sorbate solutions were prepared by dissolving dry individual compounds in the appropriate solvents. The sample volume was 20 μL.

Physicochemical characteristics and retention factors of studied tetrahydroquinoline derivatives

No.	Formula	Solvent	E_{solvs} kJ/mol	μ, D	V, A^3	S_{app}, A^2	α, A^3	$\log P$	k^* (ODS)	k^* (PGC)
1		—	—	2.27	209.6	63.40	17.85	1.74	0.02	2.64
		Water Acetonitrile	32.35 31.44	3.28 3.25	211.7 211.7	57.07 57.12	23.37 23.20			
2		—	—	4.17	230.6	59.89	19.44	0.86	1.03	1.24
		Water Acetonitrile	47.72 46.31	6.02 5.96	230.9 230.9	60.06 60.10	25.50 25.32			
3		—	—	4.47	339.9	84.17	30.16	3.21	7.81	50.76
		Water Acetonitrile	36.49 35.45	6.36 6.30	340.3 340.3	83.88 83.92	39.84 39.54			
4		—	—	2.01	229.9	68.67	19.58	1.77	3.46	14.42
		Water Acetonitrile	29.60 28.75	3.08 3.05	232.9 232.9	63.92 63.91	25.47 25.29			
5		—	—	4.94	234.9	68.70	20.11	0.92	1.31	3.54
		Water Acetonitrile	41.20 40.16	6.34 6.30	235.0 235.0	68.63 68.63	26.03 25.86			
6		—	—	5.46	211.8	64.22	18.35	0.81	0.82	1.20
		Water Acetonitrile	42.16 41.07	7.17 7.12	212.1 212.1	63.86 64.22	23.86 23.70			
7		—	—	4.49	214.8	62.23	18.15	0.45	0.79	1.68
		Water Acetonitrile	41.03 40.00	5.76 5.73	214.9 214.9	62.22 62.22	23.52 23.36			
8		—	—	4.72	235.1	67.29	19.85	0.79	1.12	1.90
		Water Acetonitrile	40.84 39.80	6.03 6.00	235.2 235.2	66.72 66.72	25.60 25.43			
9		—	—	5.10	255.1	73.75	21.79	1.26	1.32	6.61
		Water Acetonitrile	40.83 39.78	6.58 6.55	255.3 255.3	72.04 72.05	28.11 27.92			
10		—	—	6.41	305.6	79.46	27.21	3.96	12.29	34.88
		Water Acetonitrile	42.81 41.60	8.70 8.64	305.9 305.9	79.84 79.80	35.69 35.44			

* The composition of the eluent was acetonitrile and water in a ratio of 4 : 6 vol/vol.

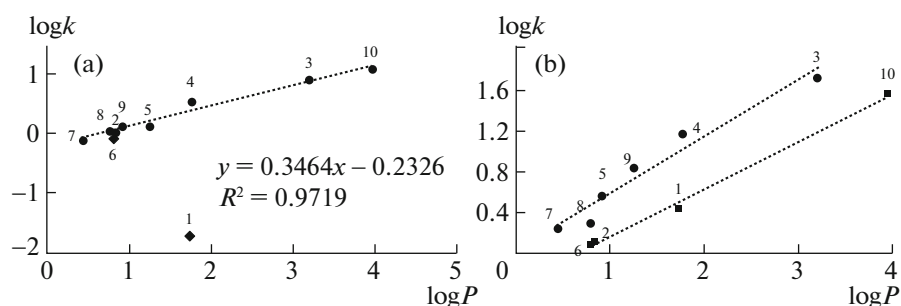


Fig. 1. Dependences of the retention factor of tetrahydroquinoline derivatives on the sorbates' lipophilicity: (a) ODS, (b) PGC. The content of acetonitrile in the eluent was 40 vol %.

The magnitude of the retention factor was used to characterize the retention of compounds [9]. Sodium nitrite was selected as the compound not sorbed.

Molecule geometry was optimized and the physicochemical parameters of the sorbates were calculated by the density functional method in the B3LYP/6-31G basis set using the Gaussian 09 software package. The PCM model was used to consider solvation effects. The area of the projection of the molecules onto the plane was calculated with the Marvin Sketch software [10]. The values of the molecular volume (V), the maximum area of the projection onto the plane (S_{app}), the polarizability (α), the dipole moment (μ), and the solvation energy (E_{solv}) of the tetrahydroquinoline derivatives are shown in the table.

RESULTS AND DISCUSSION

The main structural element of the studied compounds is a tetrahydroquinoline fragment that combines an aromatic ring and a saturated heterocycle; it is characterized by an extended conjugated system and nonplanar geometry. Presence of substituents leads to additional redistribution of the electron density, and to a change in geometrical characteristics of the molecules.

It is known from liquid chromatography theory that retention on nonpolar sorbents is determined mainly by the sorbate dispersion interactions with the stationary phase. It is therefore determined by such analyte characteristics as the volume of a molecule, its polarizability, and its lipophilicity [9].

Our data show that the sorption of tetrahydroquinoline derivatives on PGC and ODS generally follows the patterns of retention in RP-HPLC. However, the competing interactions of multifunctional tetrahydroquinones and polar eluent complicates the processes in a chromatographic system and results in deviations from the RP mode patterns. The sorbates' retention factors on PGC are much higher than those on ODS, due probably to the aromatic fragment of their molecules participating in specific interactions with the easily polarizable electron systems of the sp^2 -hybrid

carbon atoms of the PGC surface [8]. The differences between retention on the sorbents are especially obvious for compounds containing no groups that actively interact with the eluent (e.g., compounds **3** and **4**).

The graph in Fig. 1a presents the linear dependence typical of the RP mode for retention on ODS and the lipophilicity of sorbates (see table). The deviation of the point corresponding to compound **1** in the graph is probably due to the ability of the carboxyl group to participate in specific interactions with eluent components that shift the acid–base balance in an aqueous acetonitrile mixture. The presence of other functional groups capable of interacting with the eluent (hydrazide, hydroxyl, and the chlorine atoms in compounds **1**, **2**, **6**, **10**) results in two correlation series in the graph of the dependence between lipophilicity and the retention factor on PGC (Fig. 1b). The retention of these compounds is weaker than that of other sorbates, despite their similar lipophilicity. Compound **1** is retained on PGC more strongly than on ODS, due probably to the ability of the sorbent carbon surface to participate in specific interactions with carboxyl and other polar groups. The corresponding point on the graph thus deviates much less from the general dependence in [8].

In general, the dependences between retention on PGC and polarizability, and the area of molecule projection (Figs. 2a, b), are also typical for the RP mode; i.e., retention grows along with the values of these characteristics. The symbasis of the changes in the values of retention on PGS and the sorbates' dipole moment (Fig. 2c) could be a result of the polar retention effect during the sorption of compounds **2**, **5**, and **7–10**, which contain polar ester groups at position 4 and oxo groups at position 2. Deviations of the points corresponding to other sorbates from the given dependences are probably due to features of the spatial and electronic structure of the functional groups of these compounds. Thus, the oxo groups in compounds **5–9**, in contrast to the methyl radicals in compounds **1–4**, largely shifts the electron density from the C2 atom of the heterocycle, while there is almost no charge on the carbon of the hydroxymethyl groups in compound **6**,

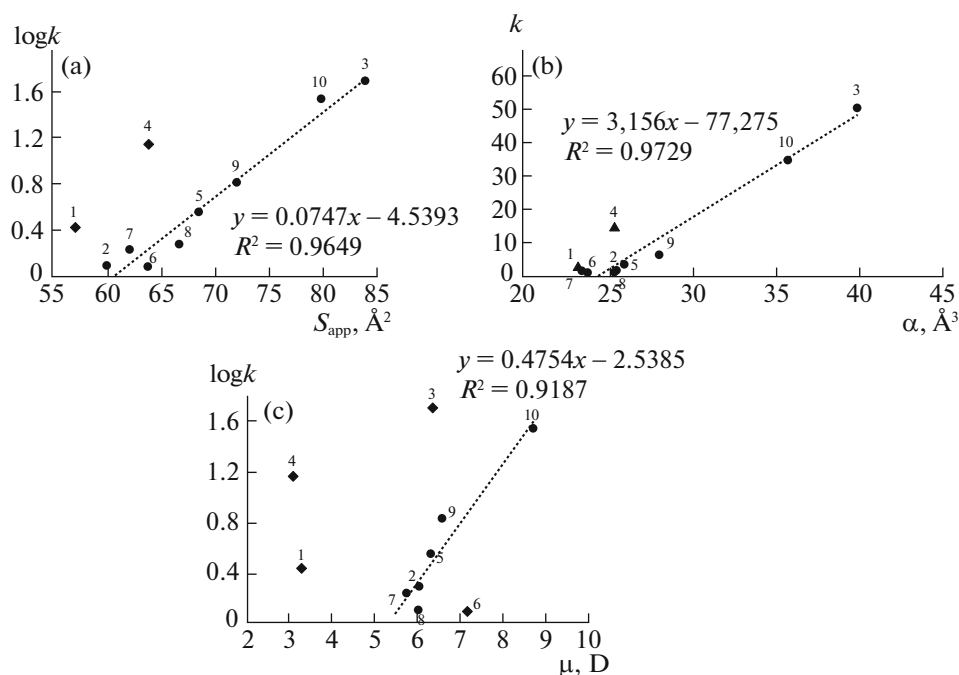


Fig. 2. Dependences of the retention factor of tetrahydroquinoline derivatives on (a) the maximum projection surface, (b) polarizability, and (c) dipole moment. The sorbent was PGC; the content of acetonitrile in the eluent was 40 vol %.

compared to the carbon of the ester and carboxyl groups (Fig. 3).

As was noted above, the presence of a polar substituent in the sorbate molecules increases their competitive interaction with the polar eluent and thus lowers retention. The data presented in the table show that the latter factor plays a substantial role in the chromatographic behavior of tetrahydroquinoline derivatives. A substance with functional groups capable to specific interactions with an eluent's polar components is thus retained less (compounds **1**, **2**, **5–9**). However, the nature of the functional group barely affects retention; i.e., the retention factor is altered slightly when with a carboxyl group is replaced with a hydrazide group on methyl derivatives (compounds **1** and **2**), and by a hydroxymethyl or ester group on the oxo derivatives of tetrahydroquinolines (compounds **6–8**). The most important factor in the interaction between these compounds and the eluent is the presence of a protonated nitrogen atom and carbonyl group at position 2.

At the same time, the polarity of an eluent (like its chemical nature in general) promotes the association and solvation processes in the bulk of the mobile phase. This in turn could shift the equilibrium in the chromatographic system, changing the retention characteristics of the analyte. It is known from the literature that the probability of such processes in aqueous acetonitrile solutions is particularly high [11, 12].

The data presented in the table show that the physicochemical characteristics of the compounds, calcu-

lated for a vacuum and a solvent medium, differ little from one another, and are almost the same for water and acetonitrile. The slight difference between the energy of solvation of the tetrahydroquinoline derivatives with polarity comparable to that of the solvents, is mainly due to the structure of the analyte molecules. Figure 4 shows that the energy of solvation correlates poorly with the dipole moments and polarizability of the sorbates, characteristics that determine the orientation and intermolecular dispersion forces. This is probably due to the predominant role of donor–acceptor interactions with the eluent, as is indirectly confirmed by the abovementioned lower retention of the heterocycles containing protonated nitrogen atoms. The higher (by almost 150%) solvation energy of 2-methyl-1,2,3,4-tetrahydroquinoline-4-carbohydrazide (compound **2**), compared to its ester analog (compound **4**), can be also explained by the effect of these interactions. At the same time, compound **4** is retained on ODS nearly 300% longer than compound **2** (and by almost 1000% on PGC).

Introducing the methyl radical at position 6 into the tetrahydroquinoline molecule has virtually no effect on the solvation energy of the corresponding derivatives (compounds **5** and **7**; **8** and **9**), due probably to the minor role of dispersion interactions in the eluent solution; it does, however, slightly increase the retention factor.

Replacing the methyl radical at position 2 with an oxo group greatly increases the dipole moment of the compounds and their energy of solvation by compo-

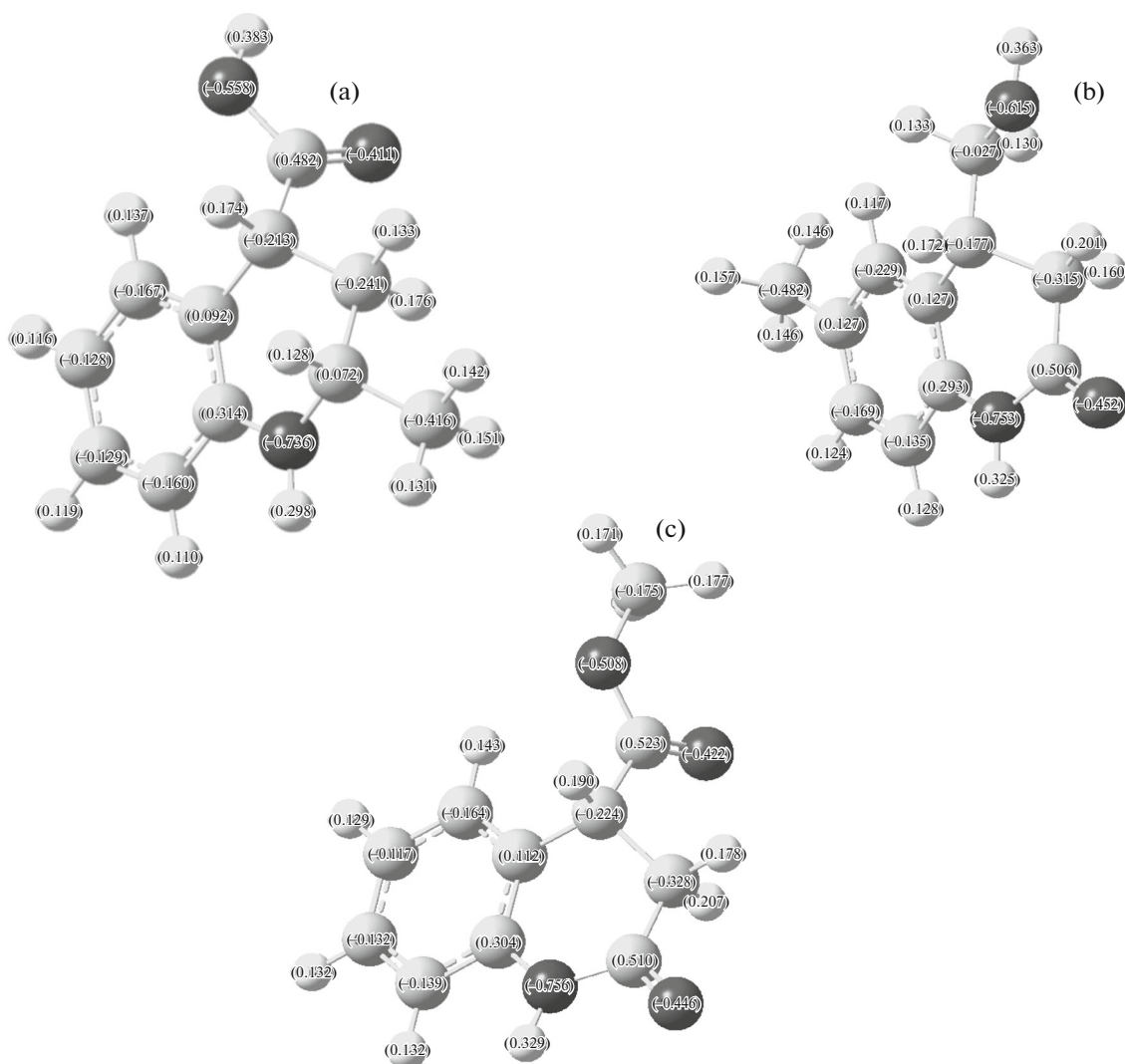


Fig. 3. Mulliken atomic charges in the molecules of the investigated compounds: (a) compound **1**, (b) compound **6**, and (c) compound **7**.

nents of the mobile phase. As was noted above, oxo derivatives are thus retained more weakly than their methyl-containing analogs (compounds **4** and **7**). Thus, even slight elongation of the hydrocarbon radical in the ester group, followed by an increase in the polarizability and lipophilicity of the corresponding compounds, enhances dispersion interactions with the sorbent and improves retention. In addition, ethyl almost completely shields the associated oxygen atom, preventing specific interactions with the mobile phase, as is confirmed by the lower solvation energy and greater retention of ethyl esters (compounds **8** and **9**), compared to the corresponding methyl esters (compounds **5** and **7**).

Introducing a phenyl radical into tetrahydroquinoline greatly increases the volume, lipophilicity, and polarizability of the molecule, and thus enhances dispersion interactions with the sorbent, resulting in the high values of the retention factors of compounds **3**

and **10** on both sorbents. This is probably also due to the considerable increase in energy consumption for the formation of the cavities for introducing bulky hydrophobic molecules into the polar solvent's structure. The maximum values of the retention factor of these compounds on PGC are also due to the ability of phenyl radicals to participate in π -interaction with the delocalized electron density of the carbon surface. It is interesting to note that during the transition from ODS to PGC, the order of these compounds' elution changes; i.e., compound **3** is first eluted on ODS, and compound **10** eluted on PGS. This is probably due to features of their spatial structure. The area of compound **3**'s projection onto the plane is slightly greater than that of compound **10**, increasing the area of its contact with the flat surface of PGC and thus strengthening the interaction between the sorbate and the sorbent. The sorbate surface area is not as import-

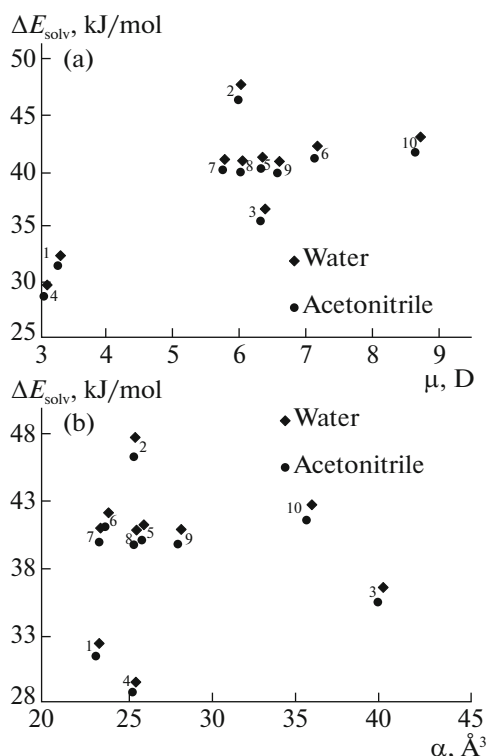


Fig. 4. Dependences of the sorbates' energy of solvation on their (a) dipole moments and (b) polarizability.

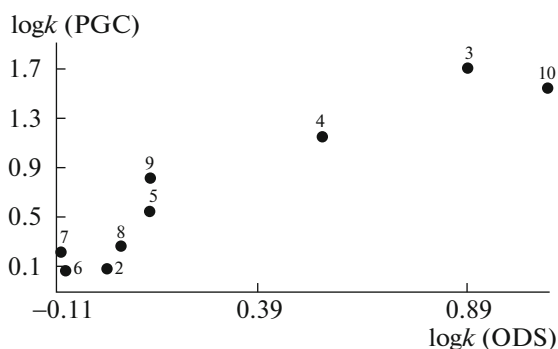


Fig. 5. Correlation between the values of sorbate retention on PGC and ODS (content of acetonitrile in the eluent, 40%).

ant for retention on ODS, which is why compound **10** is retained more strongly on it.

Differences between the sorption mechanisms of both nonpolar sorbents are shown by the graph in Fig. 5 and are described by the equation

$$\log k_A = a + b \log k_B,$$

where k_A and k_B are the retention factors on sorbents A and B, respectively [9]. As is well known, the greater the deviations from this dependence, the more the retention mechanisms on the selected sorbents differ.

The almost complete lack of a correlation between the retention factors of sorbates on PGC and ODS indicates differences in the mechanisms of tetrahydroquinoline derivative retention on these generally non-polar sorbents. Retention on ODS is due primarily to dispersion interactions; with PGC, sorption is probably the result of specific (polar) interactions that do not occur on ODS (Fig. 5).

CONCLUSIONS

Despite the RP mode used in chromatography, the retention of the tetrahydroquinoline derivatives depends strongly on the structure of the sorbates and the presence of functional groups, their nature, and their spatial arrangement. PGC also exhibits much higher sensitivity to the molecular geometry and polarity of substituents than ODS.

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