Gas chromatographic indicator of the ability of five- and six-membered heterocyclic nitrogen-containing compounds for self-association in pure liquids

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The retention indices of five- and six-membered nitrogen-containing heterocyclic compounds (pyrrole, pyrazole, imidazole, 1,2,4-triazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,3,5-triazine, isoxazole, and oxazole) were determined on a capillary column with the OV-101 nonpolar stationary phase. The difference between the experimentally determined boiling point of the sorbate and that calculated from GC data ($\delta T_{\rm b.p.}$) was proposed as a gas chromatographic indicator sensitive to the ability of substances to form self-associates in pure liquids.

Key words: capillary gas-liquid chromatography, five- and six-membered heterocyclic nitrogen-containing compounds, retention indices, self-association of sorbate, gas chromatographic indicator of self-association.

Previously,[1—3] during investigations devoted to the search for the regularities of the gas chromatographic behavior of heterocyclic nitrogen-containing compounds, we have studied aromatic heterocycles, including pyridines, pyrazines, oxazoles, thiazoles, and some substituted imidazoles. The influence of substituents on the retention time of heterocycles was examined, and additive schemes for the calculation of retention indices of these compounds on capillary columns with different polarities were offered. The schemes take into account that the contributions of individual substituents in different positions relative to the heteroatom are nonequivalent.[2]

The purpose of this work is the search for a dependence of retention indices determined on a nonpolar capillary column on the physicochemical properties of five- and six-membered heterocyclic aromatic compounds. In addition, it is of interest to compare the gas chromatographic retention parameters of heterocycles with their ability for self-association in neat liquids and to find a gas chromatographic indicator of this ability.

Experimental

Gas chromatographic analysis was carried out on a Pye Unicam 104 chromatograph with a flame-ionization detector (the chromatograph was adapted for work with capillary columns) and a glass capillary column (0.3 mm×50 m) with the OV-101 nonpolar liquid phase prepared according to the procedure described previously.[4] The thickness of the phase layer was $d_{\rm f}$ = 0.4 μm, the temperature of analysis was 110 °C, and the temperature of the injector and detector was 200 °C. Helium was used as the carrier gas, and the split ratio of the gas flow was 1 : 30. For the calculation of retention indices, the "hold up time" was determined from the retention of methane, injected into the column with a sample of *n*-alkanes C_6—C_{12}. Samples (0.2—0.4 μL) of 1—2% solutions of heterocyclic compounds in diethyl ether (whereas imidazole was dissolved in benzene) were analyzed.

Standard samples of pure compounds listed in Table 1 were purchased from Fluka, Sigma, Aldrich, Merk-Shuchardt, and Reakhim.

Results and Discussion

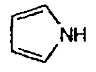
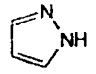
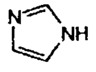
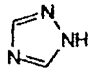
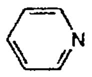
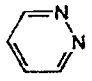
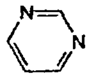
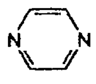
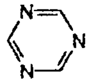
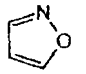
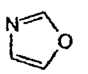
The main physicochemical parameters of nonsubstituted five- and six-membered aromatic heterocyclic compounds and their retention indices are presented in Table 1.

The molecules of the compounds studied are shaped as planar cycles whose geometric parameters, electron density distribution, and physical and physicochemical parameters are available from the reference literature[5—8] and original works.[9—12] Comparison of the published data shows that the introduction of additional heteroatoms into the nitrogen-containing cycle affects the polarizability, dipole moment, acid-base properties, and other parameters of the molecules, which has an effect on the values of retention indices on a nonpolar column packed with OV-101 (see Table 1).

In GLC analysis of polar substances on a column with a nonpolar liquid phase, the partial molar free energy of the interaction of the sorbate with this phase is mainly determined by the dispersion and induction interactions.[13] The energy of the intermolecular interac-

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 730—733, April, 1999.

Table 1. Physical and physicochemical parameters of five- and six-membered aromatic nitrogen-containing heterocyclic compounds[5,7,9–11] and their retention indices

Compound	B.p. /°C	$\bar{V}_m$* /cm^3	α (au)	μ /D	$I^{110}_{\mathrm{OV\text{-}101}}$ (i.u.)	$\delta T_{\mathrm{b.p.}}$ /°C
	130	69.4	54.9	1.74	747	+19
	187	68.0	49.3	2.21	864	+45
	256	66.1	49.2	3.84	1042	+73
	260	—	43.8	2.72	1116	+61
	115	80.9	61.5	2.22	739	+6
	208	72.6	53.8	4.22	915	+54
	123	78.8	53.8	2.33	744	+13
	118	77.7	56.1	0	722	+14
	—	—	47.7	0	663	—
	94	64.1	42.3	2.76	590	+28
	70	65.8	43.0	1.50	538	+21

* The molar ratio $\bar{V}_m$ was calculated by the formula $\bar{V}_m = M/d$, where M is the molecular weight, and d is the density of the substance.

tion is proportional to the static polarizability α of interacting molecules, their ionization potentials (*IP*), dipolar moments (μ), and molar volumes ($\bar{V}_m$).

As can be seen in Table 1, the five-membered heterocycles exhibit a nonadditive change in the retention indices as the number of N atoms in the molecule increases, for example, on going from pyrrole to pyrazole and 1,2,4-triazole. The position of N atoms in the cycle also substantially affects the retention index. In particular, the presence of the "pyridine" N atom in the α-position to the "pyrrole" nitrogen results in an increase in the retention index by 117 units (*cf.* indices of pyrazole and pyrrole), and its transition to the β-position corresponding to the transition from pyrazole to imidazole gives an increase of 178 i.u. Pyrazole and imidazole are characterized by almost the same values of polarizability α, close values of the molar volume $\bar{V}_m$ (see Table 1), and close ionization potentials *IP*,[14] but differ substantially in retention indices: 864 and 1042 i.u., respectively. This cannot be related entirely to the difference in the values of dipole moments μ of these compounds, which result in an additional contribution of the inductive component to the total energy of the interaction of the sorbate with the liquid phase. This contribution usually does not exceed 10% for chromatography of polar substances on the nonpolar liquid phase. The order of GC elution of another pair of compounds (imidazole and 1,2,4-triazole) correlates with neither polarizability, nor dipole moments. Pyridine possesses a significantly higher polarizability than pyrazole, and the dipole moments of these heterocycles virtually do not differ. Nevertheless, the retention index of pyridine is 125 i.u. lower than that of pyrazole. One more pair of compounds (isoxazole and 1,2,4-triazole) is a more striking example of noncorrespondence of their GC retention values and physicochemical parameters of sorbate molecules: despite close values of the dipole moments and polarizabilities, their retention indices differ by almost twice.

Let us consider the influence of the number and mutual arrangement of N atoms in six-membered aromatic heterocycles on the their GC behavior. The polarizability values α decrease as the number of N atoms in the cycle increases.[10] Symmetrical triazine is characterized by the lowest α value. It possesses the zero dipole moment and, hence, has the lowest (in this group) retention index, which is close to that of benzene determined under the same conditions.[15] However, these substances differ substantially in the α and *IP* values: the polarizability of benzene is considerably higher than that of 1,3,5-triazine,[10] whereas the latter has higher values of ionization potentials.[7] The mutual compensation of these factors in the absence of specific interactions with the stationary phase results in the fact that the values of retention indices of these substances on the nonpolar column are close. As in the case of five-membered cycles, the mutual arrangement of N atoms has a strong effect on the retention. For example, in the group of diazines, pyrazine with a zero dipole moment has the lowest retention index. Bringing together of N atoms is accompanied by an increase in the dipole moment and retention index: the jump is 171 i.u. on going from pyrimidine to pyridazine. Pyridazine has an anomalously high boiling point as imidazole (see Table 1).

Thus, the expected order of increasing the energies of the dispersion and induction interactions of the sorbates with the stationary phase does not coincide with the real sequence of elution of the five- and six-membered cycles containing one, two, and three N atoms. This is most likely due to the difference in the vapor pressure at the temperature of analysis, *i.e.*, this is related to the thermodynamic parameters of substances in the pure liquid and in solutions in the nonpolar phase under conditions of infinite dilution during chromatography.

We assumed that the difference between the energy of evaporation of the pure liquid and the sum of the energy of transition from the gas phase to the liquid stationary phase and the energy of solution of individual molecules in the nonpolar liquid phase under conditions of infinite dilution plays the main role in the specific features of sorption of these compounds. It is known[16,17] that in gas chromatography the partial molar free energy of sorption ΔG_S is negative and can be divided into two parts, one of which corresponds to the energy of sorption in the ideal solution ΔG_V and the other corresponds to the excess partial molar energy of mixing ΔG_E related to a change in the free energy of sorption when one mole of sorbate is mixed with the stationary phase at the temperature of analysis:

$$-\Delta G_S = \Delta G_V + \Delta G_E. \qquad (1)$$

Equation (1) is valid only for "ideal" substances, which do not form associates in pure liquids. In this case, the energy of evaporation of the pure liquid and the energy of transition from the gas phase to the stationary liquid phase during chromatography are equal and differ in sign only. However, the compounds under study are characterized by the ability to form associates in a pure liquid. The energy $\Delta G'_V$ necessary for evaporation of one mole of substance from the pure liquid can be described by the sum

$$\Delta G'_V = \Delta G_{ass} + \Delta G_V, \qquad (2)$$

where ΔG_{ass} is the partial molar free energy spent in the transformation of one mole of associate into individual molecules, and ΔG_V is the partial molar free energy of evaporation in the transition of individual molecules from the pure liquid to the gas phase.

Comparison of Eqs. (1) and (2) shows that $|\Delta G_V| < |\Delta G'_V|$, because the individual molecules (not their associates) are removed from the vapor phase to the liquid stationary phase. This difference between ΔG_V and $\Delta G'_V$ allows one to obtain information on the ability of substances to self-associate in the pure liquid using GLC.

The boiling temperatures of pure liquids reflect the energy of evaporation of one mole of sorbate from the pure substance, and the boiling points of the sorbate calculated from the retention parameters reflect the energy of evaporation of the sorbate from its solution in the stationary phase containing no associates.

It is known that substances are eluted according to their boiling points during analysis on a column with the nonpolar stationary phase. This dependence is especially well fulfilled in the case of hydrocarbons that exhibit no polar interactions with the phase and give no associates in the pure liquid. If the retention indices of the substance and boiling points of n-alkanes taken for its calculation are used for the determination of gas chromatographic boiling points, the $T_{b.p.}{}^{GC}$ values obtained differ from the experimentally determined boiling points of these compounds $T_{b.p.}$ by the value of

$$\delta T_{b.p.} = T_{b.p.} - T_{b.p.}{}^{GC}. \qquad (3)$$

For the compounds studied, we calculated $T_{b.p.}{}^{GC}$, using the scale of n-alkanes, by the equation

$$T_{b.p.}{}^{GC}(X) = T_{b.p.}(C_n) + \\ + \frac{T_{b.p.}(C_{n+1}) - T_{b.p.}(C_n)}{100}(I_X - 100n), \qquad (4)$$

where $T_{b.p.}(C_n)$ and $T_{b.p.}(C_{n+1})$ are the boiling points of n-alkanes between which substance X is eluted, and I_X is the retention index of substance X.

The $\delta T_{b.p.}$ values obtained are presented in Table 1. For all the compounds studied, the experimentally determined boiling points, which depend on the degree of association of the pure substance, are higher than the $T_{b.p.}{}^{GC}$ values calculated by the data of gas chromatography, *i.e.*, $\delta T_{b.p.} > 0$. The $\delta T_{b.p.}$ values vary from 6 °C for pyridine to 73 °C for imidazole.

The ability to self-associate is most pronounced for the compounds in which high dipole moments are combined with strong proton-donor and proton-acceptor properties,[12,18,19] resulting in the formation of intermolecular hydrogen bonds. Associates of pyrazole are two- and three-unit nonstrained cycles,[7] and imidazole and 1,2,4-triazole form linear or macrocyclic oligomers in which the number of units reach 20 and more molecules.[20,21] Molecules of aromatic heterocycles are capable of stacking interactions resulting in associates in the form of stacks.[22,23] It is probable that weak hydrogen bonds exist between the pyrrolic proton (in pyrrole) or hydrogen atom of the cycle and the π-electron system of the adjacent molecule, and π—π-interactions between the cycles are also probable.[7,24]

Thus, the $\delta T_{b.p.}$ value reflects the total effect rather than the difference in the value of the free energy of evaporation from the pure liquid and the energy of condensation to the liquid phase under conditions of infinite dilution. The calculated $T_{b.p.}{}^{GC}$ value also depends on the ΔG_E value. On the nonpolar column, the ΔG_E value is due to the induction component of the energy of intermolecular interactions of the sorbate with the liquid phase; however, its contribution is insignificant.

The $\delta T_{b.p.}$ value calculated from the GLC data depends mainly on the energy of association of the sorbate in the pure liquid. Therefore, when studying self-association of substances, all measurements should be carried out on the nonpolar liquid phase only.

The $\delta T_{b.p.}$ values obtained indicate that the five- and six-membered heterocycles are most likely arranged by the energy of associate formation in the following order: imidazole > 1,2,4-triazole > pyridazine > pyrazole > isoxazole > oxazole > pyrrole > pyrazine ≈ pyrimidine > pyridine.

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Received October 14, 1997;
in revised form September 28, 1998