The influence of alkyl substituents on the chromatographic indicator of self-association of *N*-containing heterocyclic compounds

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The chromatographic indicator of the ability of substances to form associates in a pure liquid $\delta T_{\text{b.p.}}$ proposed in our previous study was used to estimate the capacity for self-association of alkyl-substituted imidazoles, pyrazoles, pyrroles, oxazoles, isoxazoles, pyridazines, pyrimidines, pyrazines, and pyridines. Alkyl substituents introduced in heterocyclic compounds decrease the $\delta T_{\text{b.p.}}$ values, which is consistent with the data on the heats of self-association of heterocyclic compounds in pure liquids. The reasons for the difference between the boiling point of a compound at standard pressure and its "gas-chromatographic boiling point" are discussed.

Key words: capillary gas-liquid chromatography, alkyl-substituted *N*-containing heterocyclic compounds, retention indices, chromatographic indicator of self-association of a substance.

Previously[1] we have proposed the chromatographic indicator $\delta T_{\text{b.p}}$ for evaluating the capacity of substances for self-association in pure liquids. Using unsubstituted heterocyclic compounds like pyrrole, pyrazole, imidazole, 1,2,4-triazole, isoxazole, oxazole, pyrazine, pyrimidine, and pyridazine as examples, we demonstrated that the value of this indicator is correlated with the strength of the associate.

The chromatographic indicator of association is calculated from the boiling points of associated heterocyclic compounds measured directly and the gas-chromatographic parameters characterizing the dispersion interaction of monomeric molecules with the molecules of a nonpolar stationary phase.

In this work, we have studied the influence of alkyl substituents in five- and six-membered nitrogen-containing heterocyclic compounds on the gas-chromatographic indicator of association of these substances in pure liquids.

Experimental

Gas-chromatographic analysis of methylated heterocyclic compounds listed in Tables 1—3 was performed at 110 °C on a glass capillary column[2] with OV-101 polymethylsiloxane; the layer thickness was d_f = 0.4 μm. The temperatures of the flame ionization detector and injector were 200 °C. The excess pressure of the carrier gas (helium) was 1 atm; the gas split ratio was 1 : 30. The "dead time" was determined for methane, injected together with a sample. The sample size was 0.2—0.4 μL of a 1—2% solution of a heterocyclic compound in diethyl ether or benzene. Samples (1 μL) were injected using a Hamilton syringe. Retention of the methyl-substituted heterocyclic compounds under analysis was characterized by Kovats indices using C_6—C_{12} *n*-alkanes as standards. Heterocyclic compounds were commercial preparations of Fluka, Sigma, Aldrich, Merk-Shuchardt, and Reachim. *N*-Alkyl-substituted pyrroles, imidazoles, pyrazoles, and *N*-ethyl-1,2,4-triazole were prepared by alkylation using a known procedure.[3]

The gas-chromatographic indicator of the capacity of substances for self-association $\delta T_{\text{b.p.}}$ and gas-chromatographic boiling points $T_{\text{b.p.}}{}^{\text{GC}}$ were calculated from equations proposed previously.[1]

The resulting values are listed in Tables 1—3.

Results and Discussion

Self-association of the molecules of nitrogen-containing heterocyclic compounds is due to donor—ac-

Table 1. Retention indices and the $\delta T_{\text{b.p.}}$ values for methyl-substituted azoles

Compound	$T_{\text{b.p.}}$/°C	$I^{110}_{\text{OV-101}}$	$\delta T_{\text{b.p.}}$/°C
2-Methylimidazole*	267	1050	+84
4(5)-Methylimidazole*	263	1198	+47
1,2-Dimethylimidazole*	204	1006	+29
3(5)-Methylpyrazole	204	930	+46
4-Methylpyrazole	207	964	+41
3,5-Dimethylpyrazole	218	1010	+42
5-Methylisoxazole	122	702	+23
3,5-Dimethylisoxazole	143	801	+17
2,4,5-Trimethyloxazole	135	830	+2
1,2,5-Trimethylpyrrole	173	976	+5

*Retention indices were determined previously[11] at 150 °C.

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Table 2. Retention indices and the $\delta T_{\text{b.p.}}$ values for *N*-alkyl-substituted heterocyclic compounds

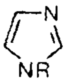
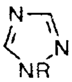
Compound	R	$T_{\text{b.p.}}$/°C	$I^{110}_{\text{OV-101}}$	$\delta T_{\text{b.p.}}$/°C
		Imidazoles		
	Me	198	929	41
	Et	226	991	54
		Pyrazoles		
	Me	127	743	17
	Et	137	809	9
		1,2,4-Triazoles		
	Et	199	900	48
		Pyrroles		
	Me	113	731	6
	Et	129	803	3
	Pr	145	886	2.5

Table 3. Retention indices and the $T_{\text{b.p.}}$ and $\delta T_{\text{b.p.}}$ values for six-membered heterocyclic nitrogen-containing compounds

Compound	$T_{\text{b.p.}}$/°C	$I^{110}_{\text{OV-101}}$	$\delta T_{\text{b.p.}}$/°C
Pyridazine	208	915	54
3-Methylpyridazine	215	982	45
4-Methylpyridazine	225	1045	42
3,6-Dimethylpyridazine	215	1052	31
Pyrimidine	123	744	13
4-Methylpyrimidine	141	827	9
5-Methylpyrimidine	153	864	11
Pyrazine	118	722	14
2-Methylpyrazine	135	812	6
Pyridine	115	748	3; 5*
2-Methylpyridine	129	814	1; 1*
3-Methylpyridine	144	—	5*
4-Methylpyridine	145	864	4; 6*
2,3-Dimethylpyridine	163	941	2
3,5-Dimethylpyridine	170	974	2

*The correspoinding retention indices of pyridines determined on SE-30 polymethylsiloxane at 110 °C.[13]

ceptor π...π interactions and to the formation of hydrogen bonds.[4] The stronger the associates formed in a pure liquid, the greater the energy needed for evaporation and the higher the boiling point determined experimentally ($T_{\text{b.p.}}$). During evaporation in a chromatograph, the associates are destroyed. Under conditions of infinite dilution in a chromatographic column, monomeric molecules of a sorbate interact with molecules of the stationary phase (SP). If a nonpolar phase is employed, the interactions are mainly of the dispersion force type; the contribution of the induction component is insignificant. Chromatographic separation in a column starts with the transfer of individual molecules of a substance (sorbate) from the vapor phase to the liquid stationary phase followed by interaction of the sorbate with the stationary phase (sorption). Therefore, the vapor pressure of a self-associated substance above a pure liquid differs from that in a chromatographic column. Evaporation of a pure liquid consisting of nonpolar molecules, for example, *n*-alkanes, requires the energy ΔG_{v}. Having entered a capillary column from the injector, the molecules of an *n*-alkane condense from the vapor to liquid and interact with the nonpolar phase. The energy ΔG_{v} absorbed during vaporization is thus liberated. In this particular case, the overall energy of sorption (ΔG_{s}) is equal to the sum of ΔG_{v} and the excess energy of mixing (ΔG_{E}). The ΔG_{E} value for the interaction of *n*-alkanes with polymethylsiloxane is close to zero; therefore, the vapor pressure above a pure liquid is virtually equal to that in a chromatographic column at a specified temperature. Hence, the boiling point of an *n*-alkane calculated from chromatographic data ($T_{\text{b.p.}}^{\text{GC}}$) is close to the known $T_{\text{b.p.}}$ value measured directly.

In the case where a compound forms associates in the pure liquid, association between molecules should be considered. The energy of vaporization ΔG_{v}^{*} comprises the energy needed to destroy the associates (ΔG_{ass}) and the energy required to vaporize the individual molecules of the pure liquid (ΔG_{v}). Monomeric molecules rather than associates enter the column. In the sorption process conducted under conditions of infinite dilution, the sorbate molecules interact with the nonpolar phase. The resultant energy of sorption ΔG_{s} is the sum of the condensation energy, numerically equal to the energy of vaporization of individual molecules, and the excess energy of mixing ΔG_{E}, which in the case of polar substances, accounts for no more than 10% of ΔG_{s}. Thus, the energy absorbed during vaporization of an associate ΔG_{v}^{*} is greater than the energy of ΔG_{s} and the vapor pressure above an associated liquid p° is lower than that in a gas-chromatographic column at the same temperature.

The difference between ΔG_{v}^{*} and ΔG_{s} provides information on the capacity of a sorbate for self-association in the pure liquid using gas chromatography. For practical purposes, it is sufficient to compare the boiling points of sorbates calculated from retention indices with the known experimental boiling points of their pure liquids.

Determination of the retention indices actually involves simulating the behavior of a hypothetical *n*-alkane with a fractional number of carbon atoms. The elution sequence of *n*-alkanes from a column with a nonpolar SP corresponds to the boiling points. Therefore, the relationship between the retention indices and the boiling points of *n*-alkanes can be used to calculate the gas-chromatographic boiling points of the compounds of interest. If a compound forms associates in the pure liquid, the $T_{\text{b.p.}}^{\text{GC}}$ values found from gas-chromatographic data should be lower than the real $T_{\text{b.p.}}$ values found experimentally for pure liquids. The difference between these values can serve as an indicator of association. A correlation between the $\delta T_{\text{b.p.}}$ value and the heat of association of a substance was first observed for unsubstituted heterocyclic compounds in our previous study.[1] The $\delta T_{\text{b.p.}}$ values for six unsubstituted five-membered heterocyclic compounds are compared (see below).

Published data[4,7–10] on the structure and strength of the associates agree with the differences between the boiling points. For example, imidazole forms the strongest associates, which are oligomers comprising up to 20 units. The corresponding heat of association is ΔH_{ass} = -7.4 kcal mol^{-1} (see Ref. 9). Imidazole is characterized by the greatest $\delta T_{\text{b.p.}}$ = 73°. For pyrrole associates, ΔH_{ass} = -1.6 kcal mol^{-1} (see Ref. 7), and accordingly, the indicator shows the lowest value, $\delta T_{\text{b.p.}}$ = 19°.

Compound	$\delta T_{\text{b.p.}}$/°C
Imidazole	73
1,2,4-Triazole	61
Pyrazole	45
Isoxazole	28
Oxazole	21
Pyrrole	19

In the imidazole and its *C*-methylated derivatives presented in Table 1, nitrogen bears an H atom capable of forming self-associates due to hydrogen bonding. The introduction of Me groups into the imidazole ring sharply changes the value of the chromatographic indicator of self-association (see Table 1). If the Me group is located between two N atoms (in position 2 of the ring), the chromatographic indicator acquires the maximum value, equal to 84°. The Me group in this position is known to increase the electron density on the N atoms and, hence, the tendency for the NH...N and NH...π interactions is enhanced. Therefore, a higher heat of association of 2-methylimidazole should be expected and its associates should be stronger than those for unsubstituted imidazole. The Me substituents in 4(5)-methylimidazole and 1,2-dimethylimidazole create steric hindrance and, hence, hamper or make impossible the formation of H bonds; this decreases the strength of associates in pure liquids. Conversely, under conditions of GLC, the presence of Me groups in positions 1,2 and 4(5) of imidazole increases the energy of dispersion interaction with a nonpolar SP. These two factors influence the $\delta T_{\text{b.p.}}$ value, which decreases from 84° to 29° for substituted imidazoles (see Table 1). Comparison of the found $\delta T_{\text{b.p.}}$ values with the published[10] heats of association in pure liquids shows that the heat of self-association of 1,2-dimethylimidazole (ΔH_{ass} = -1.8 kcal mol^{-1}) is four times lower than that for imidazole. Thus, the indicators of association in pure liquids ($\delta T_{\text{b.p.}}$) and the ΔH_{ass} values characterizing the strength of associates formed by imidazole and methyl-substituted imidazoles vary in the same order.

Pyrazoles, like imidazoles, have an active H atom capable of forming associates due to H-bonding. Interestingly, the introduction of one or two Me groups into the pyrazole ring barely changes the chromatographic indicator of self-association. Apparently, in this case, heats of association in pure liquids are also close. Only the heat of self-association of 3,5-dimethylpyrazole can be found in the literature,[9] ΔH_{ass} = -6.7 kcal mol^{-1}.

The introduction of Me groups into isoxazoles and oxazoles, having no active H atoms, decreases the capacity for self-association in pure liquids due to steric hindrance and increases the energy of intermolecular dispersion interaction with the nonpolar SP. The $\delta T_{\text{b.p.}}$ values decrease from 23° to 17° in the sequence isoxazole—5-methylisoxazole—3,5-dimethylisoxazole (see Table 1). 2,4,5-Trimethyloxazole, apparently, does not form associates at all.

If the "pyrrole" nitrogen in di- or triazole is alkylated, the indicator of self-association $\delta T_{\text{b.p.}}$ markedly decreases (see Table 2); the capacity for self-association also decreases. For instance, *N*-methylation of imidazole decreases the enthalpy of association from -7.4 to -2.2 kcal mol^{-1} (see Refs. 9, 10).

Pyrroles differ from other azoles by the fact that they virtually do not exhibit basic properties. *N*-Methyl-, *N*-ethyl-, and *N*-propylpyrroles are characterized by low $\delta T_{\text{b.p.}}$ values. Apparently, these compounds either do not form self-associates by the π...π-interaction mechanism due to steric restrictions or the energy of their formation is very low and has almost no effect on the $\delta T_{\text{b.p.}}$ values. The boiling points of pyrroles measured directly are close to the boiling points calculated from the gas-chromatographic data (see Table 2).

Six-membered aromatic *N*-containing heterocyclic compounds are known to be associated in pure liquids.[12] Dimeric and polymeric associates as "stacks" (stacking structures) are formed due to dipole—dipole and π...π interactions. Stacking structures can be linked to one another by H-bonds formed by the lone electron pair of an N atom of one ring with the α-H atom of another ring. Table 3 presents the retention indices and the $\delta T_{\text{b.p.}}$ values of pyridazine, pyrimidine, pyrazine, pyridine, and their methylated derivatives. Unsubstituted pyridazine has the highest value of the chromatographic indicator; the introduction of a Me group in position 3 or 4 of the ring decreases the $\delta T_{\text{b.p.}}$ value by 9—12°, while the introduction of two Me groups decreases the $\delta T_{\text{b.p.}}$ value by 23°. This type of variation of $\delta T_{\text{b.p.}}$ indicates that the strength of associates of methyl-substituted pyridazines in pure liquids should change in the same order.

Pyridines come last among the six-membered nitrogen-containing heterocycles presented in Table 3 regarding the capacity for association. Pyridine dimerizes in the pure liquid. The crucial role in the association of pyridines belongs to dipole—dipole and π...π donor-acceptor interactions between the aromatic rings.[12] A ^{1}H and ^{13}C NMR study of associates formed by pyridine and its methylated derivatives showed that the stability of the associates varies in the sequence 4-methylpyridine > pyridine ≥ 3-methylpyridine > 2-methylpyridine > 2,6-dimethylpyridine.[13] It can be seen from Table 3 that the $\delta T_{\text{b.p.}}$ values change in the same order.

Thus, the results obtained indicate that the chromatographic indicator of association of substances in pure liquids changes upon introduction of alkyl substituents to the N or C atoms in five- and six-membered nitrogen-containing heterocyclic compounds. This change in $\delta T_{\text{b.p.}}$ correlates with the strength of self-associates of heterocyclic compounds formed in pure liquids. The chromatographic method proposed for the evaluation of the capacity of sorbates for self-association in pure liquids based on $\delta T_{\text{b.p.}}$ values is feasible and readily available. This makes this technique especially attractive compared to other labor-consuming and expensive physicochemical methods such as calorixzmetry and ^{1}H and ^{13}C NMR and IR spectroscopy.

References

1. R. V. Golovnya, T. E. Kuz'menko, and I. L. Zhuravleva, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 730 [*Russ. Chem. Bull.*, 1999, **48**, 726 (Engl. Transl.)].
2. R. V. Golovnya, A. L. Samusenko, and E. A. Mistryukov, *J. High Resol., Chromatogr. CC*, 1979, **2**, 609.
3. A. F. Pozharskii, V. A. Anisimov, and E. B. Tsupak, *Prakticheskie raboty po khimii geterotsiklov* [*Practical Works on the Chemistry of Heterocycles*], Izd-vo Rostovskogo Universiteta, 1988 (in Russian).
4. A. F. Pozharskii, A. D. Granovskii, and A. M. Simonov, *Usp. Khim.*, 1966, **35**, 2, 261 [*Russ. Chem. Rev.*, 1966, **35** (Engl. Transl.)].
5. B. L. Karger, *Anal. Chem.*, 1967, **39**, 24A.
6. G. Guiochon and C. L. Guillemin, *Quantitative Gas Chromatography*, Elsevier, Amsterdam—Oxford—New York—Tokyo, 1988.
7. *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, Eds. A. R. Katrizky and C. W. Rees, Pergamon Press, Oxford, 1984, **3**, **4**.
8. *Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982—1995*, Ed. R. C. Storr, Elsevier Sci., 128.
9. G. A. Kurkchi and A. V. Iogansen, *Zh. Fiz. Khim.*, 1991, **65**, 1240 [*Russ. J. Phys. Chem.*, 1991, **65** (Engl. Transl.)].
10. Yu. A. Teterin, L. N. Talanova, L. N. Nikolenko, and A. A. Popov, *Zh. Obshch. Khim.*, 1976, **46**, 1427 [*J. Gen. Chem. USSR*, 1976, **46** (Engl. Transl.)].
11. R. V. Golovnya, I. L. Zhuravleva, and M. A. Sal'kova, *Zh. Analit. Khim.*, 1992, **47**, 1269 [*J. Anal. Chem. USSR*, 1992, **47** (Engl. Transl.)].
12. F. Torrens, J. Sanchez-Marin, and F. Tomas, *J. Chem. Res. Synop.*, 1990, **6**, 176.
13. I. Wawer and S. Warycha, *Pol. J. Chem.*, 1985, **59**, 565.
14. A. L. Samusenko and R. V. Golovnya, *Chromatographia*, 1988, **25**, 531.

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