Relationship of energy characteristics and the Randic indices of imidazole and some azolides of sulfonic acids with chromatographic retention

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Imidazole and some newly synthesized imidazolides and triazolides of sulfonic acids were investigated by reversed-phase chromatography. The Randic indices, the total energies of molecules, and the energies of the transition states to hydrolysis of imidazolides and triazolides in a neutral medium were calculated. Correlations between these parameters and the retention factors were elucidated.

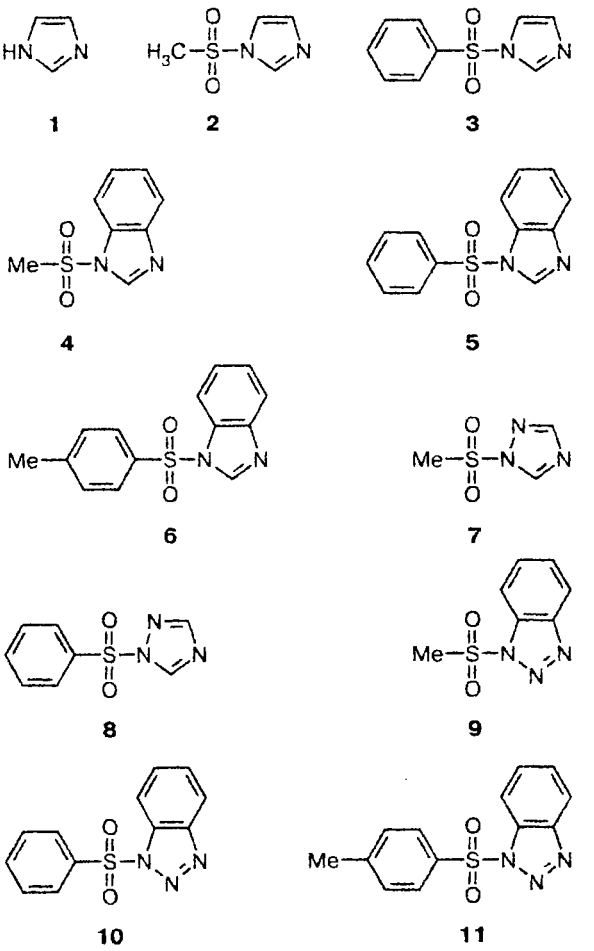
Key words: reversed-phase chromatography, biologically active substances, azoles, imidazolides of sulfonic acids, triazolides of sulfonic acids, structure—property relationship.

In recent years, there has been a renewed interest in the elucidation of relationships between the chromatographic behavior and the biological activity of nitrogen-containing heterocyclic compounds.[1—4]

In this work, we studied imidazole and some imidazolides and triazolides of aromatic and aliphatic sulfonic acids (**1**—**11**).

These objects were chosen due to the fact that some five-membered nitrogen-containing heterocycles exhibit biological activities[5,6] and imidazole and triazole are structural fragments of many biologically active compounds of natural origin: pyrine, histidine, ureides, cyanocobalamine, *etc.*[7,8] At present, there exist data indicating that it is the nitrogen-containing ring that determines the main biological response.[9] Studies[10,11] have led to the conclusion that the objects studied possess different types of biological activities and pharmacological effects.

This work is devoted to the chromatographic behavior of imidazole and some derivatives of imidazole and triazole sulfonic acids and to identification of the relationship between chromatographic retention values, a structure parameter (Randic index), the total energy of molecules, and the energy of the transition state to hydrolysis in a neutral medium.



Experimental

The chromatographic experiment was carried out under reversed-phase chromatography conditions on a Milichrom-4 microcolumn liquid chromatograph with a UV spectrometric detector at wavelengths of 190 and 220 nm. The column used (length 80 mm, inner diameter 2 mm) was filled with Separon

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SGX RPS silica gel (specific surface area 320 $m^2 g^{-1}$, particle size 5—7 μm) with bonded octadecyl groups. Degassed anhydrous ethanol was used as the mobile phase; the eluent flow rate was 45 μL min^{-1}.

Compounds **1—11** were synthesized at the chair of organic chemistry of Samara State University.[12,13] Substances to be studied were dissolved in ethanol, and the freshly prepared solutions were injected into the column using a microliter syringe. The sample size was 1 μL. The retention factor k for each sorbate was determined from the experimental results using the relation

$$k = t'_R/t_m, \quad (1)$$

where t'_R is the reduced retention time (s) and t_m is the retention time of a nonsorbable compound (s).

The retention time of a nonsorbable compound t_m was determined from the equation[14]

$$t_m = t^2_{R(2)} - t_{R(1)}t_{R(3)}/(2t_{R(2)} - t_{R(1)} - t_{R(3)}), \quad (2)$$

where $t_{R(1)}$, $t_{R(2)}$, and $t_{R(3)}$ are the retention times of neighboring homologs of *n*-alkanes.

The homologs used were heptane, octane, and nonane. The retention times of *n*-paraffins were measured by indirect UV detection[15] by adding benzene to the eluent.

Quantum-chemical calculations were performed using the HyperChem program[16,17] for individual molecules. The total energy of the molecule (E) and the energy of the transition state to hydrolysis (E_{ts}) of the N—S bond in a neutral medium were calculated. The structures of molecules were described using a topological descriptor, the Randic index $^1\chi$. This index was calculated using the bond matrix.[18,19] Each nonhydrogen atom i was characterized by the value L_i, which corresponds to the number of atoms attached to it, except for hydrogen atoms; a π bond was taken into account by adding unity to the L_i value.

Table 1. Retention factors (k) and Randic indices ($^1\chi$) of compounds **1—11**

Compound	k	$^1\chi$
Imidazole (**1**)	0.58	1.81
Methanesulfonic acid imidazolide (**2**)	0.61	2.88
Benzenesulfonic acid imidazolide (**3**)	0.64	4.59
Methanesulfonic acid benzimidazolide (**4**)	0.62	4.29
Benzenesulfonic acid benzimidazolide (**5**)	0.63	5.71
p-Toluenesulfonic acid benzimidazolide (**6**)	0.65	6.41
Methanesulfonic acid 1,2,4-triazolide (**7**)	0.33	2.88
Benzenesulfonic acid 1,2,4-triazolide (**8**)	0.48	4.59
Benzenesulfonic acid benzotriazolide (**9**)	0.47	4.29
Methanesulfonic acid benzotriazolide (**10**)	0.56	5.71
p-Toluenesulfonic acid benzotriazolide (**11**)	0.53	6.41

Note. The error of determination of retention factors does not exceed 1%.

Then the P_i values, equal to the products of L_i for two neighboring atoms were calculated and the square root (C_i) from each P_i value was extracted. The sum of all C_i gives the topological Randic index $^1\chi$.

The retention factors and the Randic indices for compounds **1—11** are listed in Table 1.

Results and Discussion

The Randic index characterizes some fundamental properties of molecular structure.[20,21] It is often included in the so-called QSAR (Quantitative Structure—Activity Relationship) equations,[18,22] which reflect the functional correlation between two sets of numerical values characterizing the structures and properties of molecules. This allows describing the properties of molecules using descriptors, which take into account significant features of molecular structure. These equations can be employed to describe *a priori* the properties of compounds, which enables targeted synthesis of compounds, in particular, synthesis of products with predictable biological activity.

Figure 1 presents the dependence of the retention factors for the sorbates under study on the Randic indices. It is clear that retention increases with an increase in $^1\chi$. It can be easily seen that these two parameters for these compounds obey a satisfactory correlation (the correlation coefficient r for imidazole and its derivatives is 0.9278 and that for triazole derivatives is 0.9091).

To elucidate the structure—property relationship, it is of interest to consider the dependence of the total energy of the molecules of these compounds on the Randic indices. It can be seen from Fig. 2 that these parameters correlate with each other; the correlation coefficient r for imidazole and its derivatives is 0.9973 and that for the triazole derivatives is 0.9919. Figure 3 indicates that the total energy increases in the same series of substituents as the retention factor (the correla-

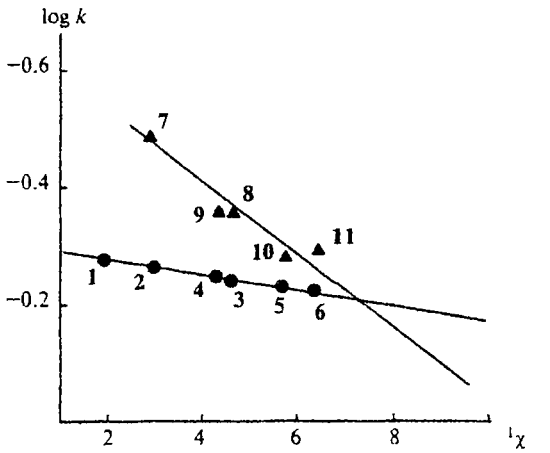

Fig. 1. Logarithms of the retention factors of compounds **1—11** *vs.* the Randic index.

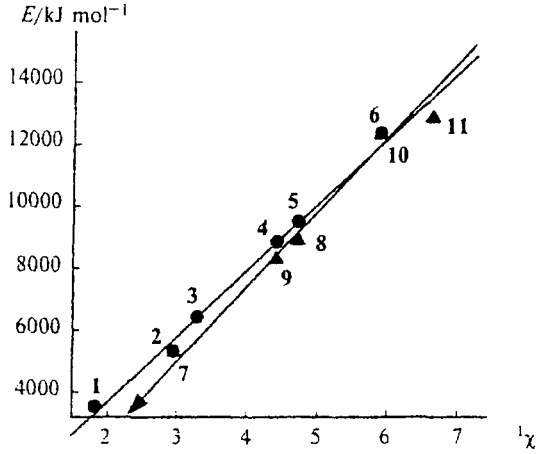

Fig. 2. Total energy of the ground state of molecules **1**—**11** *vs.* the Randic index.

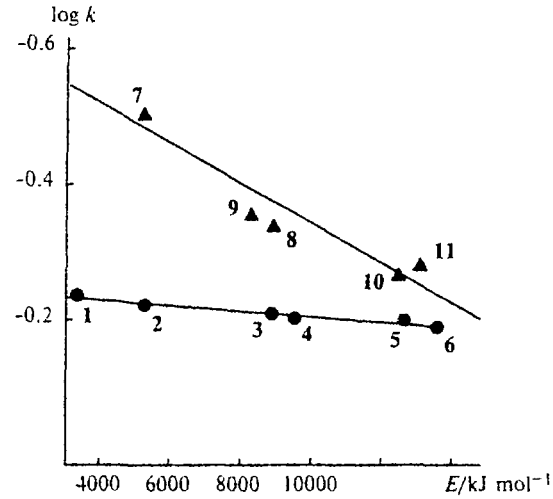

Fig. 3. Logarithms of the retention factors *vs.* the total energy of the ground state of molecules **1**—**11**.

tion coefficient r for imidazole and its derivatives is 0.8239 and that for the triazole derivatives is 0.9213). The energy of the transition complex in the hydrolysis of the azolides under consideration in a neutral medium also obeys a satisfactory correlation with the retention factor. It follows from Fig. 4 that the correlation coefficient r for imidazole and its derivatives is 0.8441 and that for the triazole derivatives is 0.9316. It is evident that retention increases with an increase in the transition state energy. This implies that the retention of these azolides is inversely proportional to their susceptibility for hydrolysis in a neutral medium.

Thus, it was shown that chromatographic retention values of the azolides of aliphatic and aromatic sulfonic acids are in good agreement with a topological characteristic of the molecule, the Randic index, and can serve as the basis for elucidation of the relationship between retention and the structures of compounds.

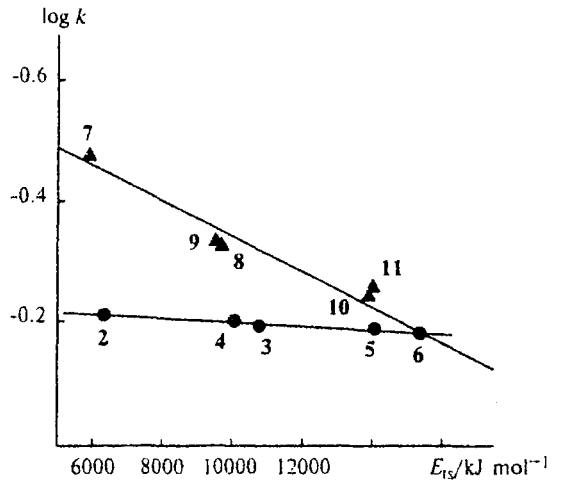

Fig. 4. Logarithms of the retention factors *vs.* the energy of the transition to hydrolysis of azolides **2**—**11** in a neutral medium.

The Randic index obeys a satisfactory correlation with the total energy of the ground state of the molecules of imidazole and the azolides of the aliphatic and aromatic sulfonic acids studied here and with the energy of the transition state to hydrolysis of these azolides in a neutral medium. In combination with the dependences of the transition state energy on the retention factor, these correlations make it possible to characterize the ability of azolides to enter into hydrolysis, including that in biological media (with pH 5—7).

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